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GENERAL PRACTICE CLINICS

VOL. 168 NO. 11 NOVEMBER 1955

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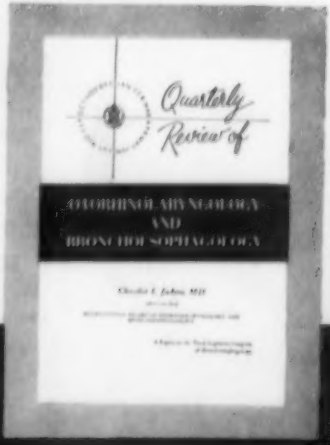

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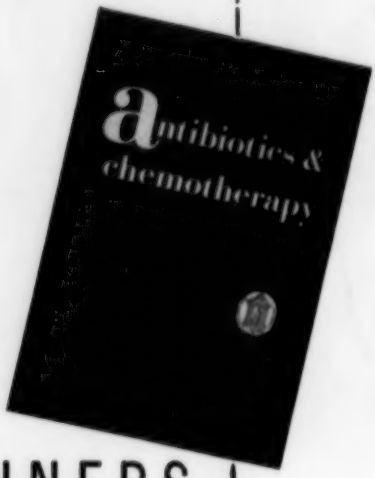

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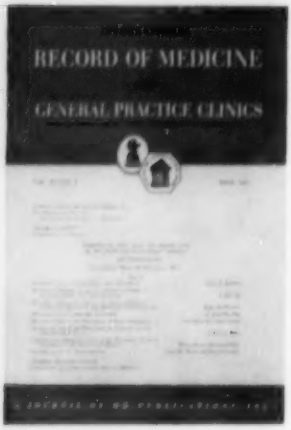

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INTERNATIONAL RECORD OF MEDICINE

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Irving Innerfield

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Part II*

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* Part I of the **Symposium on Trichomoniasis** was published in the September, 1955, issue of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS. The following papers were included: "Vaginal Cytology in *Trichomonas* Infestation" by George N. Papanicolaou and Wanda H. Wolinska; "The Recurrence of *Trichomonas vaginalis* Vaginitis" by William Filler; "Tyrothricin in the Treatment of Vaginitis Due to *Trichomonas vaginalis*" by William E. Barfield; and "Trichomoniasis in the Male" by John W. Draper.

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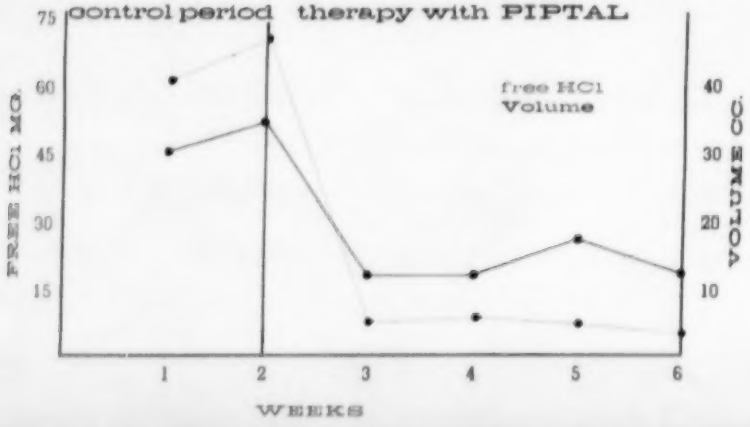

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The Rationale of Parenteral Trypsin Therapy*

Irving Innerfield, M.D.

DEPARTMENT OF MEDICINE, NEW YORK MEDICAL COLLEGE
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NEW YORK, N. Y.

I became engrossed in enzyme chemistry several years ago while evaluating alterations in protein clotting constituents produced by trypsin.[1] It had been generally agreed that trypsin, in small doses, shortens the clotting time.[2] This particular observation, based primarily on in vitro studies, stimulated my initiation into this field. I decided to investigate the physiologic effects of graded doses of in vivo trypsin. A very simple experiment was devised in which prothrombin, AC globulin, antithrombin, fibrinogen, clotting time, bleeding time, and fibrinolytic changes were serially determined during stipulated periods in the course of intravenous infusions of trypsin in rabbits and dogs.

Two important observations were made. The first was that small, slowly given parenteral doses of trypsin had no effect whatever on the clotting mechanism and produced surprisingly few and quite insignificant side effects.[3] This was contrary to the generally prevailing view that trypsin was highly toxic;[4] caused intravascular coagulation;[5] and produced shock,[5] necrosis,[6] sloughing of tissue,[6] and sensitivity reactions.[6] The second important finding related to the pharmacodynamic action of small parenteral doses of trypsin in reversing acute inflammation.

In this presentation, I shall review salient physiologic, biochemical, pharmacologic, and clinical effects of small parenteral doses of trypsin.

BASIC STUDIES

In my early studies, all clotting proteins were temporarily destroyed following rapid administration of intravenous trypsin. Twenty-four hours later each clotting constituent had returned to normal levels, with one exception. Antithrombin, exhibiting a rebound phenomenon, continued to rise progressively. This interesting observation formed the basis for employing antithrombin measurements as a test

* Lecture delivered at the Annual Teaching Seminar, Valley Forge Heart Institute, February 21, 1955.

for acute pancreatitis. As the work on plasma antithrombin casts significant light on the relationship between trypsin and a naturally occurring plasma proteolytic enzyme system, I shall devote some time to this subject.

To understand the role of trypsin in acute pancreatitis, three fundamental observations must be borne in mind: (1) many of the major signs and symptoms of acute pancreatitis depend on increased systemic absorption of trypsin; (2) trypsin, like streptokinase and other proteolytic enzymes, has been known to activate precursor fibrinolytic enzymes present in the blood and other tissues; and (3) beyond a certain critical point, plasma antithrombin reflects the extent of trypsin activation of a plasma fibrinolytic enzyme system.

Intravenous administration of trypsin in dogs[3] indicated that levels of plasma antithrombin and other clotting constituents were altered only after tremendous quantities of trypsin. Clinically the milder forms of interstitial or edematous pancreatitis (without sufficient acinar pathologic changes to influence appreciably the systemic absorption of trypsin) almost invariably were associated with normal antithrombin levels. These cases usually showed transitory but diagnostic elevations of the serum amylase. On the other hand, when the inflammatory process in the pancreas was extensive enough to cause acinar hemorrhage, necrosis, or suppuration, the quantity of absorbed trypsin became sufficiently high to activate the fibrinolytic mechanisms on which elevations in plasma antithrombin depend. It is precisely in this type of diffuse, extensive, severe pancreatitis that plasma antithrombin determinations find their greatest usefulness. In this type of pancreatitis antithrombin elevations remain detectable throughout the course of the illness in contradistinction to the usually evanescent serum amylase.

Furthermore, since elevated antithrombin levels can be ascribed only to acceleration in the rate of trypsin activation of fibrinolytic enzymes, the antithrombin quantities carry a high degree of specificity for the severer type of pancreatitis. For this reason, in milder forms of pancreatitis in which the amylase level is high and antithrombin is normal, unless one bears in mind the physiologic mechanism underlying antithrombin activation, the results may be considered equivocal. Studies on antithrombin, however, demonstrate the following: (1) beyond a certain critical concentration, trypsin activates a potent proteolytic enzyme system, and (2) the rise in antithrombin seems to link pancreatic physiology, specifically trypsin, with the enormously important functions of maintaining a fluid circulation and dissolving intravascular thrombi.

This new view obviously was at variance with previous concepts in which trypsin was regarded as a clot-producing agent. In the voluminous literature on proteolytic enzymes there was one repeatedly confirmed biochemical effect of trypsin that lent strong support to this new concept. I refer to the biochemical, physiologic, and clinical implications in the documented observations that both in vivo and in vitro trypsin depolymerizes fibrinogen and fibrin.

Our first endeavor was then to determine the effects of trypsin on the fibrin constituents of experimentally formed thrombi. This really started the entire project, which eventually led to our discovery that parenterally given proteolytic enzymes play a significant role in reversing inflammation. We chose a circuitous pathway to

this discovery,[3] since our original purpose was to ascertain whether trypsin would dissolve blood clots. We found that in order to influence blood clots in acute experiments using trypsin, one has to use quantities that are unphysiologic. We demonstrated effects upon thrombi, i.e., softening and digestion of fibrin, only after huge quantities (100 mg.) of trypsin. Wright and DeBakey disagreed but other workers confirmed my observations. Shingleton[4] used trypsin in experimentally induced pulmonary infarction in dogs. There were no infarctions in the trypsin-treated animals, whereas the incidence of pulmonary infarction in controls was 75 per cent. Shingleton gave massive doses of enzyme every eight hours for several days. Agress[11] introduced fibrin particles beyond an occlusion in the aorta of dogs, the fibrin lodging as an embolus in the coronary circulation. Extensive myocardial infarction developed. Complete occlusion of the coronary vessels occurred within two hours after the insult. At autopsy, 8 of the 13 control dogs showed severe, massive myocardial infarction and the remaining 5 showed mild to moderate involvement. In trypsin-treated animals, 6 of 16 showed massive infarction, whereas the remaining 10 had mild to moderate reactions.

The most impressive finding was, however, recanalization of the coronary vessels in the trypsin-treated group. These vessels could be perfused without obstruction or resistance. Microscopically, the striking change was the absence of the host clot in the involved coronary vessels in contradistinction to well-formed clots in controls.

It is important to mention that in the Agress[11] study trypsin was given in large doses for several days. Intravenous trypsin must be given in massive doses for a long time in order to dissolve clots. Yet, we observed almost immediate tissue changes long before the change in the blood clot. What were those immediate changes? They included such significant alterations as subsidence of interstitial edema, congestion, and hemorrhage following remarkably small quantities of parenteral trypsin. Long before there was any evidence of clot lysis, severely injured tissue immediately adjacent to clotted vessels remained viable in treated animals as compared with the controls.[13] In the controls, tissue infarction practically always supervened.[13]

I was far more impressed with the capacity of trypsin to maintain and preserve tissue viability in areas of extreme cellular injury than in any clot lysis potentialities. It was apparent to me that in patients with acute thrombophlebitis extensive tissue inflammation was promptly curtailed and reversed, but during the first three or four days of trypsin therapy, I was, at the time, equally convinced that regressive changes in underlying thrombi were very slight indeed.

I believe that time has borne out the validity of this basic observation. The amazingly rapid effect of trypsin and other proteolytic enzymes in reversing inflammation has now been amply confirmed,[14–18] but will trypsin therapy influence tissue undergoing infarction?

Since this audience is composed of cardiovascular specialists, let us consider the sequence of morphologic and biochemical alterations in a case of acute ventricular injury following a recent coronary thrombus. One of the earliest myocardial intracellular response to injury is endothelial swelling of capillaries in the injured zone.[24] Instead of being spindle shaped, the cells distend and become globular. Another very early host response to injury is a marked increase in capillary permeability, resulting

in almost immediate outpouring of fluid rich in plasma protein.[25] This is a very important point, since these proteins contribute significantly to the architectural characteristics of inflamed tissue, high viscosity, increased density, and a state of semicoagulation. There then follow edema, hyperemia, congestion, and an inflammatory infiltrate consisting predominantly of white cells but also red cells and some round cells. These events profoundly influence metabolic activity of the injured myocardium.

By its very nature, acutely inflamed tissue quickly assumes characteristics of acute biologic isolation. From time immemorial, an area of acute inflammation has been considered biologically static. Nature's aim obviously is total isolation of the inflamed zone. The welfare of the organism is protected at the expense of locally injured tissue. This biologic response, however, is universal and occurs irrespective of the tissue involved. Clinical situations occur, however, where this biologic isolation reaction is harmful, as, for example, when the site of injury is vital myocardial tissue. Here the inflammatory reaction itself constitutes a major threat to viability of the involved tissue. Unless we interrupt and reverse the abnormal metabolic processes in acutely injured vital tissue, the end result must be infarction.

How can we hope to cope with the problem of intravascular coagulation enzymatically? Bear in mind that basically there are two problems: (1) the blood clot and (2) the impending infarction. Should we focus attention on clot dissolution, employing large doses of proteolytic enzymes intravenously? We have already shown that this is much too time consuming and requires doses that are unphysiologic. Should we then concentrate on preventing myocardial infarction by employing small doses of proteolytic enzymes intramuscularly in order possibly to reverse almost instantly the vascular and permeability barriers within the injured tissue? Bear in mind how often myocardial infarction occurs in the complete absence of demonstrable thrombi. Certainly in the brief matter of 24, or even 72 hours, intramuscular trypsin will not significantly affect any macroscopic thrombus. Will it, however, effectively interrupt the sequence of biochemical events underlying abnormal intracellular metabolic activity in the acutely injured myocardium? The data we have accumulated lead me to believe that this is entirely possible using trypsin.

Any acutely inflamed tissue is characterized by intrinsic and extrinsic compressive changes involving capillaries. I will shortly demonstrate restoration of capillary blood flow following trypsin therapy. Another demonstrated factor, not sufficiently emphasized, is that of over-all tissue impermeability in acutely injured tissue. What makes an area of inflammation so highly impermeable? The high viscosity of an inflamed area is a function of a macromolecular jamming. That is to say, viscosity is a function of the degree of molecular polymerization. If we can hydrolyze, i.e., depolymerize, these macromolecules into small chained proteins, in other words make little molecules out of big ones, we must significantly modify a fundamental physicochemical abnormality of acutely inflamed tissue, namely, high viscosity. We have shown in one of our earliest studies,[3] reduction of the viscosity of gelatinous fluid in the inflamed zone following parenteral trypsin. We were not the first to show this important physiologic effect of proteolytic enzymes. Sherry et al[26] demonstrated the capacity of desoxyribonuclease to thin and liquefy thick, viscid, purulent

exudates in empyema and leg ulcer. This work was on a grossly visible level with direct enzyme substrate interaction. Our approach differs fundamentally, since we are actually altering physiochemical fluid characteristics on the microscopic level. The Sherry group devoted all their attention to purulent exudates accumulating in the end stage of inflammation, and they applied enzymes topically. We concentrated our attention on the initial stage of inflammation in which viscous edema rather than pus was the chief pathologic component, and we employed, parenterally, tiny doses of proteolytic enzymes.

I have long been aware that best results with intramuscular trypsin are obtained in early, acute inflammation, especially since gelatinous, interstitial edema responds so readily. I feel that the important biochemical lesion in areas of acute tissue injury is an imbalance between macromolecular proteins in varying states of degradation—coagulated plasma, edema fluid, hemorrhagic foci, and cellular debris—and the level of available proteolytic enzymes. Expressed more simply, a fundamental defect seems to be an inadequate rate of depolymerizing macromolecular proteins in areas of acute cellular injury. This protein macromolecular jamming predisposes to high viscosity and marked impermeability of involved tissue. Restoration of the required rate for proteolytic enzyme protein substrate interaction reduces viscosity, restores tissue permeability and blood flow, thereby preventing cellular necrosis and providing the bridges prerequisite to healing. This, essentially, is my notion of how small parenteral doses of trypsin reverse inflammation. The injected enzymes accelerate the turnover rate of much needed proteolytic enzymes at the site of inflammation. Physiologic events underlying the reversal of inflammation are consistent with augmented local proteolysis, viz.: thinner, more mobile fluid (decreased viscosity); increased tissue permeability; decreased blood sludging; decreased congestion; decreased hemorrhage; vastly improved tissue oxygenation; restored local tissue blood flow following removal of extraneous barriers to capillary blood flow (high viscosity fluid, cellular debris, cellular infiltrates).

Figure 1. In this study, one of our first experiments, we wished to ascertain what effect, if any, the administration of trypsin, streptokinase, and chymotrypsin would have on experimentally induced acute inflammation in rabbits. We instilled 4 drops of a 15 per cent mustard oil in mineral oil solution on the rabbit conjunctiva, and within 5 to 10 minutes we had evidence of a marked, acute inflammatory reaction as shown in this edema of the nictitating membrane. In addition, marked chemosis developed, plus lacrimation, which was profuse, within 10 to 15 minutes. We had produced signs and symptoms of an acute inflammatory reaction following mustard oil. To give you an idea of the technique we used, which is important should any of you wish to repeat it, we waited six hours and graded the reaction on a 1 to 4 plus basis after administering the mustard oil. Only the 4 plus reactors were utilized in this study. In this particular study we had 54 of the 4 plus reactors. They were divided into two groups: 27 acted as controls, and the other 27 were divided into three groups of 9 each. Nine received streptokinase, 9 received chymotrypsin, and 9 received trypsin.

Figure 2. This shows the appearance of the eye and nictitating membrane after several treatments with any of the three enzymes. This kind of result occurs in more

FIGURE 1

than 90 per cent of the treated animals. Recall the boggy, edematous, congested nictitating membrane without evidence of any landmarks, where everything was distorted. In the treated rabbit we see the normal appearance of the nictitating membrane and of the rabbit eye. There is no lacrimation. The most dramatic, the earliest, the most conspicuous, and the most prompt and consistent response in this experiment and in all our other experiments, indeed in all our clinical studies, is shown in this nictitating membrane: prompt reduction of the edema. You should think in terms of the biochemical defects following acute inflammatory insults regardless of their nature. The outpouring of fluids is the first response. This fluid is rich in plasma proteins and so has high viscosity. An enzyme that decreases the structural components, makes small amino acids out of big ones, decreases the viscosity, and encourages permeability and hemodynamic exchange, sets the stage for the reduction of edema. This is the situation morphologically. Here is where structure and function merge.

Figure 3. In spite of hyperemia, which is an initial reaction to injury, an area of acute inflammation is characterized by stasis, i.e., cessation of blood flow. The nonflowing blood within small vessels usually ruptures into the interstitial tissue and

then degenerates quickly. What happens to a blood clot? This figure shows a thrombus in the rabbit marginal ear vein with an acute perivenous inflammatory reaction. Wherever there is a blood vessel, we observe absence of blood. Large vessels had thrombi, but small vessels had none; they were compressed. There is a marked cellular exudative reaction. In this study we again treated the animals with various proteolytic enzymes, and it made no difference which we used.

Figure 4. At the end of 48 hours there was still a thrombus, though it seemed to be somewhat more uniform. This figure does not do justice to what we saw in the gross. Although there is still evidence of a thrombus, the important fact is that the perivascular structures appear healthy. The capillaries are now filled with blood. The controls, in the previous figure, showed capillaries devoid of blood, and infarction and gangrene developed in the involved ear segment. The treated animals, however, wiggled their ears beautifully at the end of a week; there was not a sign of injury. This is reminiscent of what happened with the rabbits in the eye experiment. There, the controls went on to panophthalmitis and blindness at the end of 72 to 96 hours. The treated animals in a large percentage of cases became perfectly

FIGURE 2

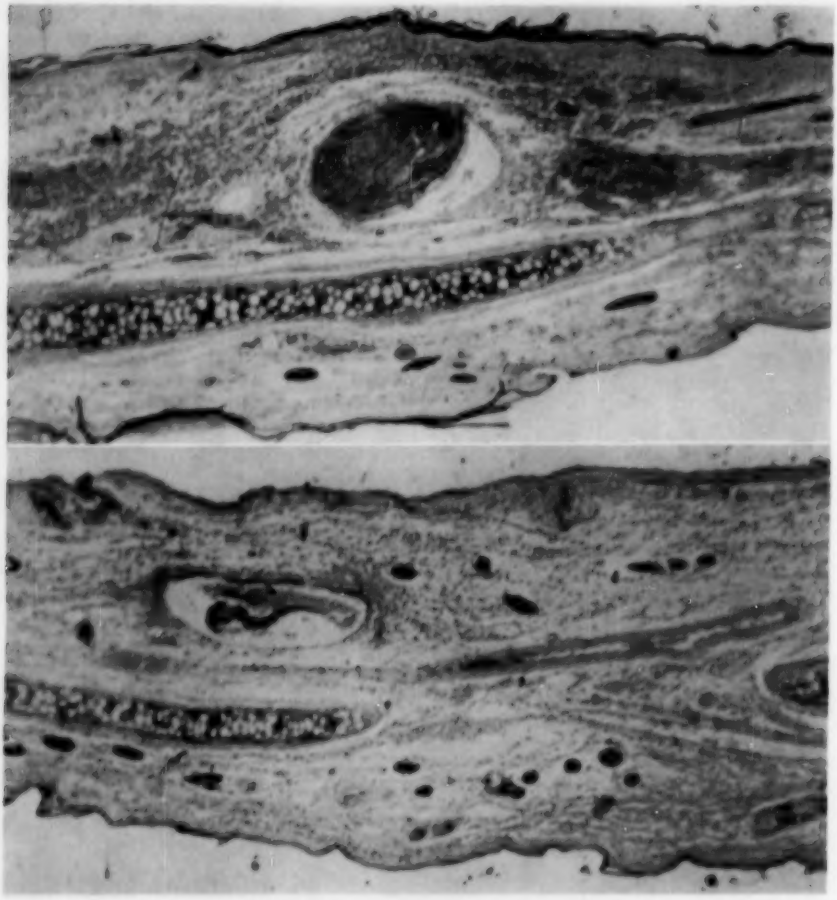

FIGURE 3 (*Top*)
FIGURE 4 (*Bottom*)

normal. We had a uniform incidence of infarction and gangrene following the injection of sodium sotradecol into the veins, the subcutaneous tissue, and the contiguous tissue, with a mass of ischemia, arterial, capillary, and venous. This figure shows how in the treated group, there was restoration of the blood and lymphatic flow; but more significantly, on a biochemical level, there was correction of the biochemical lesions caused by aberrations in proteolytic processes.

From this more recent study we formed the basic concept of reversing inflammation rather than suppressing it, as happens in cortisone or steroid therapy. We are not suppressing anything the way cortisone does. We are not suppressing mesenchymal

reactivity or the formation of fibrin or globulins. In fact, enzymes do not suppress anything, except in a sense, the end stage of cellular damage, namely, tissue necrosis. However, I think we do accelerate the rate at which proteolytic enzymes penetrate areas of inflammation. Actually we are changing, biochemically, the basic substrate protein material, which if unchanged would perpetuate impermeability. By treating with enzymes we can increase tissue permeability. Hyaluronidase is ineffective, to a large degree, in this type of inflammatory condition, although Seifter reported an anti-inflammatory or inflammatory-reversal effect following the use of hyaluronidase. Certainly hyaluronidase will do the same thing in this type of permeability experiment, but we cannot make hyaluronidase influence a leg ulcer. It did not work with the rabbit eye or in sotrocecol experiments. In this area we need an enzyme that works on a protein substrate and not on a carbohydrate or nucopolysaccaride substrate. That is where only proteolytic enzymes can be effective. Perhaps it would be wise to combine the two. Fundamentally, the change in permeability transforms an area of metabolic stasis into one of biologic dynamism and metabolic continuity, i.e., biologic continuity with contiguous tissue. The inflammatory reaction itself prejudices that type of reaction. It delimits and demarcates most effectively an area of injury from the rest of the organism. This isolation makes the tissue susceptible to eventual necrosis or suppuration. Thus nature's basic idea seems to be to get rid of the injured tissue. By introducing an enzyme,

FIGURE 5

we can prevent this and thus further control and curb the destructive processes inherent in nature.

Figure 5. Here is a type of case in which enzymes are ineffective. This patient was admitted to Metropolitan Hospital about two years ago, presenting a classical type of gangrene. She was atherosclerotic. This type of case can be given every enzyme, but life cannot be brought back into these tissues. Indeed we filled her with trypsin without success. This figure indicates the irreversibility of the end stage of inflammation, cellular injury, and necrosis. However, if therapy can be instituted before necrosis starts, the inflammation can be reversed.

Figure 6. This patient was admitted as a diabetic, with cellulitis and gangrene. He was given trypsin, but as the figure shows, there was no improvement.

Figure 7. In this case we have a different set of pathophysiologic phenomena. In the first patient (Fig. 5) the change was purely vascular, i.e., atherosclerotis, ischemia, and interruption of blood flow on an intralumenal and structural basis, and there was not much that could be done for the patient. However, in this case the cause of the ischemia or the peripheral vascular disturbance was more extravascular. Enzymes are effective in ischemia caused by perivascular inflammation, such as in diabetics with cellulitis, or by mechanical vascular compression, such as edema. In the present patient the big toe, which was necrotic, dropped off spontaneously; but the foot and leg inflammation was reversed. The leg was saved by the use of parenteral trypsin, although this patient was admitted for amputation. This was the first

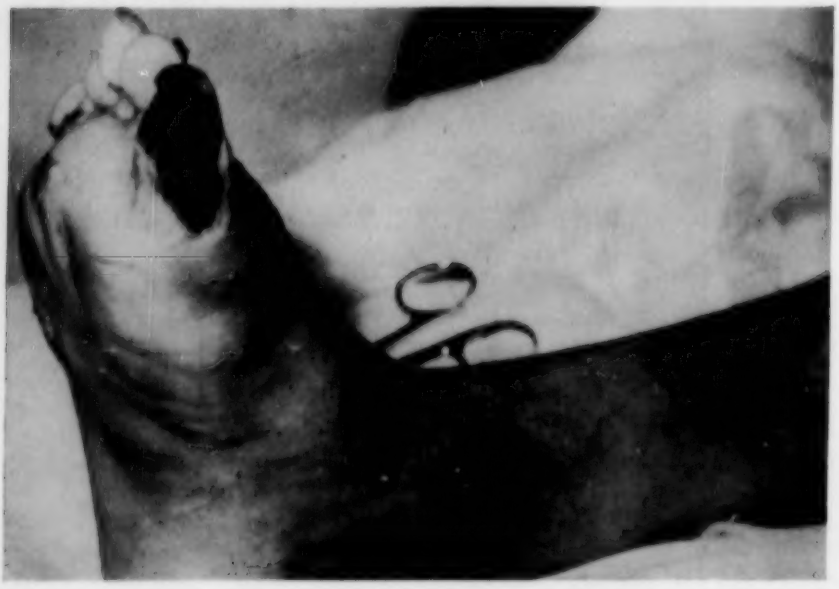

FIGURE 6

FIGURE 7

case in which I used trypsin, and it was an ideal case, for anybody would have advocated amputation of that leg. With trypsin, we had nothing to lose and everything to gain, and indeed we were able to save the leg. He is still able to use his leg and is doing well, although it occasionally flares up. When this happens he is put on Parenzyme with favorable results. These two cases demonstrate, biochemically, the important difference between ischemia resulting from extravascular inflammation, where enzymes are useful, and ischemia resulting from intrinsic, lipid, and atherosclerotic deposits, for which nothing can be done. It would certainly seem that for the type of substrate involving conjugated lipoproteins, proteolytic enzymes are not the answer. Perhaps in this case a lipolytic enzyme should be investigated, but that is outside our present field of interest. Perivascular inflammatory lesions apparently are suitable biochemical substrates for trypsin therapy.

Figure 8. We run into this type of problem frequently: a patient with an acute leg ulcer. This patient was admitted with congestive heart failure, fibrillation, hypertension, and 4 plus edema. In addition, stasis, the pressure produced by lying in bed, resulted in further tissue ischemia. She developed trophic ulcerations which broke down. An acute, red, diffuse inflammation is seen. This patient had been treated with every antibiotic known, and the service was considering amputation. At this stage a thick, adherent, purulent exudate covered the base of the ulceration, and there was a zone of extensive surrounding cellulites. The patient was put on Parenzyme, 0.5 cc. every four hours intragluteally. In hospitalized patients there is no reason

why the dose cannot be given every four or six hours, but in ambulant patients who cannot be seen that frequently, a daily injection should suffice.

Figure 9. This is the same patient seen in figure 8 24 hours later. Reversal of inflammation and crust formation is demonstrated. The crust actually began forming about two hours after the first injection; the response was so rapid that it was almost unbelievable. Enzymes seem to work with the spontaneity and rapidity of, I would say, light. It is amazing how rapidly the edema and other manifestations of acute inflammation are reversed when the right substrate, the right type of inflammation, and the right proteolytic enzyme are combined. After the enzyme is given, there is subsidence of edema, increased lymph flow, increased local capillary flow, and healing. These enzymes usually elicit a quick response, by the end of 24 to 72 hours. If there is no response by the end of 72 hours, probably there will be no change at

FIGURE 8 (*Left*)
FIGURE 9 (*Right*)

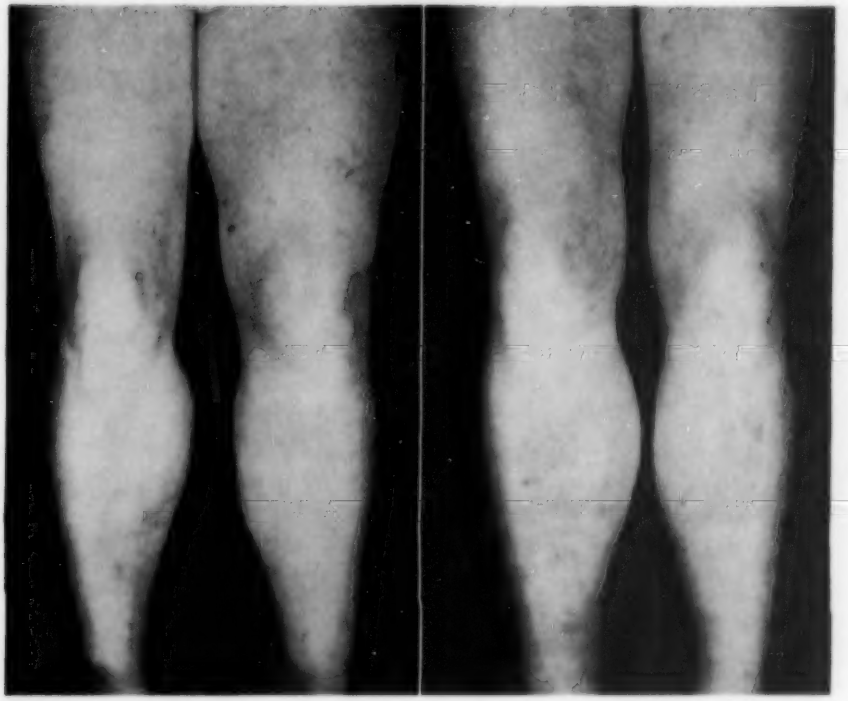

FIGURE 10 A (*Left*), B (*Right*)

all, for the enzymes work very fast. With the suitable clinical problem, intramuscular doses of trypsin produce quick reversal of inflammation.

Figures 10A and 10B. Here is one case that is very important to me: thrombophlebitis, acute, superficial, and ileofemoral. The patient refused hospitalization and was the first to be treated at home. This was his second bout with thrombophlebitis. He had been treated with anticoagulants a few years previously, was in the hospital for a few weeks, and refused to go again. Anticoagulants are no longer being used on our service, and why should they be? The question of treating him at home certainly was a reasonable one. Prothrombin times or clotting times also are no longer done, since, as shown above, small doses of trypsin have no demonstrable influence on the clotting mechanism.

Forty-eight hours later there was subsidence of edema, which was not due to Ace bandaging. This man was in bed, but the question has been raised whether these skin folds represent Ace bandaging. No, it is subsidence of edema. This also brings out a very interesting clinical point, not sufficiently recognized, that edema of the lower extremity subsides from above downward. In determining the efficacy of any of these enzymes in edema, for which they are most effective, do not measure

FIGURE 11 A (*Left*); B (*Right*)

the ankle when there is extensive involvement of the lower extremity. Instead, on the first day measure the thigh; it is here that the changes will be found. The last area to show the alteration or reversal will be at the furthermost point: the ankle or the feet, if these are involved. It is much the same story if only the leg is involved: look for changes in the region of the calf before the sole. The patient was back to work at the end of a week or so and returned to his doctor for two injections a week for about a month.

For about two years we have not hospitalized our thrombophlebitis patients; they do not need it. There is a tremendous economic saving in freeing hospital beds, eliminating cumbersome, costly laboratory work, and saving work time. Acute thrombophlebitis patients may now be successfully treated at home with Parenzyme. The recommended dose is 0.5 cc. twice daily for the first three days, then once daily for about a week or ten days.

Physician: Do you use antibiotics with these?

Dr. Innerfield: Absolutely not. Especially in this type of case, which is of non-bacterial origin. Why use penicillin or tetracycline unnecessarily? Another reason

for not using antibiotics in this study of inflammation was to exclude an important therapeutic variable. If antibiotics had been introduced, one could logically ask how we could be sure which one was effective. So they were not used in this case, nor in the patient with streptococcal infection. The enzyme alone was used.

How does the enzyme work in inflammation of bacterial origin? Does it have any bacteriolytic or bacteriostatic action? Certainly not, but the blood stream and the blood cells do; the blood phagocytes and the immune bodies in the blood do. When we restore fluid, blood, and tissue communicability and when we bring the patient's own blood back into the capillaries, bring the patient's own biologic forces back into the previously isolated, excluded area of injury, those organisms are well taken care of. The reason they can multiply during the period of inflammatory barricade is because the cellular defense mechanisms are so effectively excluded by the inflammatory reaction itself. By increasing permeability and modifying extravascular compression, we bring body defense mechanisms back into the injured area and in that way control inflammation of bacterial origin.

Figures 11A and 11B. This is the case of the 24 year old white male described in another paper;[17] presenting the problem of recurrent thrombophlebitis. Many physicians have asked if there were really thrombi present in the veins or were the veins simply dilated. The veins were loaded with thrombi, massive, palpable, grossly visible thrombi. There was possible correlation of his hypertension not only with venal caval thrombosis but also thrombotic involvement of the small, renal efferent arterial system. There was a question of tying off the vena cava, and there certainly was a problem of thrombosis that involved the deep as well as the superficial vessels. For this reason he was embolizing and his life was in constant jeopardy. When I first saw him he was in extremis, with hemoptysis and a temperature of 105 F. He also was harassed for more than a year by a severe, hacking, unproductive cough that allowed him no rest.

Figure 12. This is the same patient. You can see the same superficial vessels but they are no longer filled with thrombi. They are now dilated and superficial. The blood clots have disappeared. His coughing ceased within the first week of Parenzyme therapy and he no longer has hemoptysis. After seven weeks of daily injections, the thrombi had disappeared and at this time we stopped giving Parenzyme, in my ignorance of the mechanisms of the dynamic processes involved.

Six weeks after discontinuing trypsin, he developed a fresh thrombophlebitis. Of course this was the clue that he was a dynamic blood clotter. I mention the idea of dynamism because I think of it in terms of an altered balance—a balance between the substances that are proteolytic enzymes in nature and tend to dissolve thrombi under normal conditions. But this is a case in which the inadequate rate at which the proteolytic, clot dissolving enzymes were being elaborated was unequal to the task of dissolving the thrombi as quickly as they formed. At the end of six or seven weeks, the beneficent effect of Parenzyme therapy had been dissipated. Once again an enzyme imbalance occurred. If that idea had merit, reinstitution of therapy should again rectify the enzyme-substrate imbalance and produce thrombolysis. Indeed it did. In accordance with this concept, he has remained controlled on maintenance therapy. He has not had a single recurrence of thrombophlebitis since

we instituted the long-term maintenance therapy. He gets two shots of Parenzyme a week without interruption, to this day, and is now back at work.

Figure 13. This is again the same patient. Not only have the thrombi vanished and the inflammation subsided, but the pigmentation has disappeared. And, of course, the pigment molecule is tough and resistant to any type of therapeutic agent.

Physician: The lymphatic system does that.

Dr. Innerfield: You may be right. I do not know, but this certainly is an amazing phenomenon.

Physician: What happened to his hypertension?

Dr. Innerfield: That is another amazing thing. His hypertension was reversed. I do not know, but there is a possibility that there were thrombi in the terminal renal arterioles. Thrombolysis of large clots occurred at the end of several months, so his hypertension reversed more quickly than the large thrombi, maybe because the renal thrombi were considerably smaller. Once the circulatory obstruction and the peripheral obliterative effect, with its deleterious influence on blood pressure, were eliminated, his blood pressure returned to normal. I cannot prove that, but it is certainly an intriguing possibility. At present he is normotensive.

Physician: What is your technique of ascertaining fibrinolysis on the lymphatic level in contradistinction to the venous level?

Dr. Innerfield: Purely morphologically, by biopsies.

Physician: What about thrombophlebitis in the pregnant woman? Have you had any opportunity to see if it has any effect on the fetus or on the liver?

Dr. Innerfield: No effect whatever. In fact the problem came up not long ago in Israel. I received a cablegram from an obstetrician whose patient in the seventh month of gestation developed a recurrent thrombophlebitis. She previously had two cesarean sections and had been scheduled for another section. They of course could not employ anticoagulants. They wanted to know if they could use trypsin. We encouraged them to use Parenzyme because we had observed no deleterious effect on the pregnant state whatever. Later we learned that the patient was successfully treated with Parenzyme. A resident of Dr. David Habif, at Columbia-Presbyterian Medical Center, asked me the same question not too long ago. He too had a pregnant patient with acute thrombophlebitis. I assured him that Parenzyme was safe and I was told that excellent results were obtained.

Physician: Along the same line, would you take a patient that you had done a surgical procedure on, say a herniotomy, and who developed a thrombophlebitis and give him Parenzyme? Would you say also that it would affect the inflammatory reaction for the healing of the surgical site?

Dr. Innerfield: That question often comes up. As a matter of fact, I would like to mention Agress' paper[11] on this subject. He has studied this problem in dogs. It is his conclusion, and it bears out our observations, that wound healing is definitely facilitated by trypsin. It encourages healing rather than interferes with it. This is just the opposite of what you and I had feared. It facilitates granulation tissue growth.

Physician: Have you used it in coronary occlusions?

Dr. Innerfield: Certainly I have, although not very extensively. That is not my

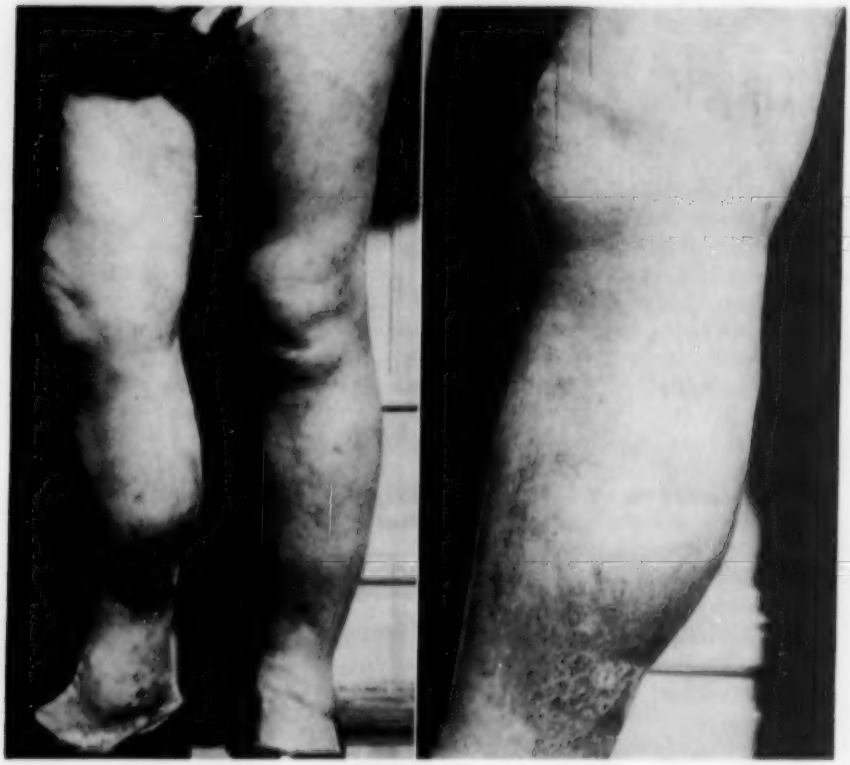

FIGURE 12 (*Left*)
FIGURE 13 (*Right*)

field of interest at the moment, but I know of several groups that are investigating that problem. All I can tell you is that it is much too early to draw any conclusions. It is a very difficult problem to evaluate statistically. There are many factors, many variables. That is why I have deliberately avoided that subject, at least for the time being. I would much rather try to elucidate the principles and mechanisms in thrombophlebitis. There are enough variables in thrombophlebitis to make it a sufficiently complex problem to occupy my thoughts. It may take many years before we are able to know how effective proteolytic enzyme therapy can be in cases of myocardial infarction. Certainly, on the basis of several related observations, which I have attempted to elucidate, I would say it is a most promising approach. Certainly it warrants looking into.

Physician: How about black eyes? Can you treat them with trypsin?

Dr. Innerfield: Hopen and Campagna have published two papers[15] on the use of Parenzyme in ocular trauma. They have mentioned such things as black eyes and

say that nothing compares with Parenzyme in rapidity of subsidence of what you would expect, edema, the coagulated blood, the tissue injury. Head injuries in general respond very well to Parenzyme. Edema following trauma is one of the best clinical indications for intramuscular trypsin.

Physician: How about chronic inflammation, as in collagenous diseases?

Dr. Innerfield: The enzyme has no value here, because collagenous tissue is the wrong substrate. To be more precise, unless there are lysine and arginine radicals, trypsin therapy is useless. Lysine or arginine are not found in collagen.

Physician: Have you used it in hemiplegia?

Dr. Innerfield: In early hemiplegia we have used it. It is one of the effective agents in reducing cerebral edema. Cerebral edema is very important in early cerebral thrombosis, and apparently responds as well to Parenzyme as edema elsewhere.

Physician: How early?

Dr. Innerfield: That is the critical factor. With a patient who has had hemiplegia for six months or for six years, Parenzyme will probably not be at all effective. But if the duration of the hemiplegia is six days, the chances are that the edema factor is still highly important. Trypsin is an effective weapon in reducing localized edema, including that following brain injury. Therefore, its use is indicated in recent cerebro-vascular accidents. It can also be used in decreasing cerebral edema in instances of cerebral hemorrhage, since it does not change clotting or bleeding time.

Physician: How about its use in periarthritis or arterial swelling of periarthritis?

Dr. Innerfield: This has to be qualified from a temporal standpoint—is it acute, subacute, or chronic? If it is an acute exacerbation, by all means use it. In the presence of acute joint swelling, its use is indicated; if there is none, the enzyme is not used. The surest way to ruin a good agent is to use it where it is not indicated. In chronic or subacute arthritis it is of no value.

Physician: Back to the mechanical problem. A dose of 2.5 mg. of trypsin intramuscularly does not give us very much trypsin to distribute equally through body tissues.

Dr. Innerfield: It is not distributed equally in all body tissues. Any area of acute inflammation is characterized by an initial increase in capillary permeability at the site of injury, in contradistinction to the degree and extent of permeability elsewhere. That is why any agent that is given will diffuse in greater quantity at the site of injury than elsewhere. A very important question that faced us was whether we were dealing with a nonspecific foreign protein anti-inflammatory effect. We used boiled trypsin, which is a protein, and got no results whatever. We know it is not a nonspecific foreign protein effect at all. We could not elicit any of these results in the rabbit eye experiment or any of the others, using boiled trypsin or streptodonase instead of streptokinase. The fundamental and important contribution of all these studies is the awareness at the present time that these enzymes are enormously effective in rapidly reversing inflammation and preventing tissue necrosis and infarction, which I think will be its greatest field of usefulness.

Physician: What about acute pancreatitis?

Dr. Innerfield: As we showed in our early studies, using antithrombin which

correlated with increased levels of trypsin, there was an enormously increased quantity of trypsin in the circulation in cases of acute pancreatitis. This is due to rupture of the acini of the involved parenchyma. It is interesting that certain severe forms of acute pancreatitis are known as acute hemorrhagic pancreatitis. This again gives the lie to the notion that trypsin is a clotting agent. Rather, it facilitates blood flow and overcomes the fibrous barriers. Acute pancreatitis is one type of inflammatory condition where trypsin is contraindicated, since there already is brisk trypsin activation. I have always been very much interested in pancreatic disturbances and have been impressed with the relative frequency of acute pancreatitis. It is a much more common disturbance than we realize. It is just that laboratory diagnostic facilities are not adequate. But the disease itself is frequent. Granted that acute edematous, interstitial pancreatitis is frequent, why is pancreatic abscess and necrosis relatively infrequent? This observation may be based upon the inflammatory reversal effects of the proteolytic enzyme system following spontaneous, endogenous trypsin stimulation.

Physician: I carry a few vials of Parenzyme in my bag routinely. Since the trypsin is in an oily base, does one have to heat the vial in cold weather?

Dr. Innerfield: No, that is never necessary.

Physician: How much more have you learned about the physiologic effects of parenteral trypsin since your first publications in 1952?

Dr. Innerfield: In my first papers[1, 2] I emphasized four significant physiologic effects of parenteral trypsin: (1) depolymerization of long chained protein molecules in inflamed areas, i.e., hydrolysis of fibrin molecules; (2) decreased viscosity of fluid elements in inflamed areas (plasma, lymph, tissue juices, exudates); (3) enhanced phagocyte effects; (4) restoration of local blood flow and metabolic continuity in acutely injured tissue. Since these early publications, additional important observations have been made: pronounced anti-edema effects; decreased blood clot viscosity; increased tissue permeability; and reduced intracapillary blood sludging.

Physician: Cortisone has been known to change a localized infection into a generalized one. What about Parenzyme in this regard?

Dr. Innerfield: Not only do inflamed areas of bacterial origin not spread following Parenzyme—and unlike cortisone—but they quickly recede. Trypsin and cortisone differ in many fundamental respects, and so the impact of proteolytic enzymes and steroid hormones upon acutely injured tissue differ. Cortisone decreases permeability; trypsin increases permeability. This is a most important basic point. Since the inflammatory reaction is designed to render the injured area increasingly impermeable, as already mentioned, the reaction can be rightly considered an effective barrier to the body's immune defense mechanisms. In other words, since the area of tissue injury eventually becomes totally impervious to lymph and blood flow, neither the patient's blood nor prescribed antibiotics get into the target area. Furthermore, owing to depressed mesenchymal reactivity, and other factors, the antibody response is lowered following cortisone. Trypsin does not have this effect. Phagocytesis, i.e., destruction of engulfed bacteria, has been related to intracellular proteolytic enzymes. The leukocytic response is usually lowered following cortisone. Cortisone suppressed the inflammatory response to injury, thereby leaving the organism vulner-

able to widespread invasion. Trypsin does not suppress the inflammatory reaction at all; but it does eliminate barriers to the essential constituent for cellular and tissue viability, namely, a restored blood supply; subsidence and reversal of inflammation quickly follow. Restoration of blood flow, following trypsin, also considerably enhances—in fact may permit for the first time—an antibiotic effect. Cortisone has no augmented antibiotic effects.

Physician: I now understand why Parenzyme injections are followed by rapid resolution of acute inflammation, especially edema. However, isn't inflammation nature's way of responding to injurious agents? Why change it?

Dr. Innerfield: Before answering your very pertinent question, I think we should attempt to define inflammation. According to Regdon the simplest definition of inflammation is "the local response of viable tissue to injury." Ehrich regards inflammation as "a disturbance in homeostasis." Opie regards inflammation as the "process whereby cells and serum accumulate about an injurious substance and tend to remove or destroy it." With full humility I should like to present my own definition of inflammation, based upon my work with trypsin. I consider inflammation as a host reaction on a local tissue level to an injurious agent, consisting of the development of biochemical conditions (low *p*H, increased viscosity, impermeability, anoxia, high carbon dioxide, increased lactic acid, high potassium, low carbohydrate) inimical to the survival of both the invaded tissue and the invading substance. It seems to me that local death of tissue following injury (suppuration, necrosis) is sometimes more consistent than elimination of the invader. Dubos has stated, "There are many cases where inflammatory processes, far from contributing to the destruction of the pathogenic agent, provide for it an environment in which it can multiply or find a shelter against antimicrobial substances, either released by the host tissue or introduced during therapy. It is well known that inflammation can bring about the release of products toxic to the host, or the destruction of some of its tissues. In the eye, for example, its price may be the permanent loss of function."

It is often desirable, and sometimes imperative, instantly to institute mechanisms designed to maintain viability of injured tissue in the presence of an acute inflammatory reaction. This can be done only by modifying the abnormal biochemistry of acutely inflamed tissue. If I have made this point clear to you, I have delineated the basic idea constituting the rationale of parenteral trypsin therapy, i.e., preservation of tissue viability in inflamed areas.

Physician: How would you characterize, biochemically, the effect of Parenzyme on inflammation?

Dr. Innerfield: Lewis, Menkin, Spector, and others have shown that the development of a full-blown acute inflammatory reaction depends upon the elaboration of certain chemical substances, viz., leucotaxin for the cellular response, histamine for permeability changes and plasma accumulation, exudin, necrosin, and others. Please observe that each of these biochemical substances relates to the elicitation of an inflammatory response. Trypsin, given parenterally, appears to provide the biochemical stimulus for reversal of the inflammatory response. Whether it does so by neutralizing, destroying, or inhibiting the chemical agents that evoke and main-

tain the response is a most intriguing possibility. In summary, one may characterize Parenzyme the biochemical mediator for reversing acute inflammation.

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Symposium on Psychiatry and Religion

Werner Wolff, Ph.D., Guest Editor

special articles by outstanding authorities on religion and psychiatry

- WERNER WOLFF: Introduction
- FRED H. BLUM: Psychiatry and Religion: A Historical Survey
- JOSEPHINE H. ROSS: A Current Contribution of Psychoanalysis to the Concept of God
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- SAMUEL GLASNER: Towards an Operational Definition of Religion
- JOSEPH MAIER: The Sociological Definition of Religion
- MORTIMER OSTOW: The Need to Believe: Quasi-Religious Attitudes in Non-Believers

The following will also be included in the December issue: an Editorial, "On Christmas and Neuroses," by Félix Martí-Ibáñez, M.D.; an Editorial Survey, "Ultrasonic Energy in Medicine;" an article, "Clinical Experience with a Sustained-Release Preparation of Reserpine," by Theodore A. Beck, M.D., and the Quarterly Review of Ophthalmology, which appears as a regular feature.

SYMPOSIUM ON TRICHOMONIASIS—PART II

Guest Editor—HERBERT S. KUPPERMAN, M.D., Ph.D.

Trichomonas vaginalis: Nutritional Requirements and Diagnostic Procedures

Alfred B. Kupferberg, Ph.D.

ORTHO RESEARCH FOUNDATION

RARITAN, N. J.

Trichomonas vaginalis, a flagellated parasitic protozoan, was first discovered in 1836 by Donne,[1] a French investigator, in the abnormal vaginal discharge of a woman suffering from vaginitis. The size of the cell is approximately that of a leukocyte, and its form, while somewhat pear-shaped, can be seen to assume diverse shapes. At the anterior end are four flagella which move with great rapidity. Along the side of the body starting from the base of the flagella and ending mid-point on the cell is an undulating membrane which also beats rapidly. Extending from the posterior portion of the cell is a stiff appendage called the axostyle.

In 1939, after three years of investigation, where others had failed, Dr. Ray E. Trussell isolated in pure culture a strain of *T. vaginalis* which is being maintained to this day in the laboratories of the Ortho Research Foundation. It is this culture which furnished so much of our accepted biologic information about *T. vaginalis*. However, it was not until the advent of antibiotics that pure cultures could be readily obtained (Adler and Pulvertaft,[2] and Johnson, Trussell, and Jahn[3]).

Very little is known about the growth factor requirements of *T. vaginalis*. The isolation of pure cultures made possible the studies of the nutritional requirements of this parasitic protozoan.

Trussell's original medium in which he successfully obtained a pure culture of *T. vaginalis* consisted of Locke's solution with the addition of 1 per cent liver infusion agar (Difco) and 5 per cent placental extract. When certain aspects of the physiology of *T. vaginalis*, such as energy requirements, optimum temperature, *p*H, and oxidation-reduction potential were established by preliminary experiments,[4–10] Johnson and Trussell[11] formulated a medium containing agar, liver infusion, maltose, cysteine, peptone, Ringer's solution, and the essential unheated blood serum. Methylene blue was added to this medium to indicate the degree of anaerobiosis in the final medium (CPLM medium).

Initial studies by Johnson and Trussell[12] in 1945 on the growth factor requirements of *T. vaginalis* showed that ascorbic acid, glutamic acid, and choline had a stimulating effect upon cell multiplication, and that where nicotinamide, folic acid,

TABLE I

Composition of Complete Trypticase Nutrient Medium for T. vaginalis*

(The amounts listed are the calculated values per 10 ml. of final medium)

Trypticase (BBL)	200 mg.	Riboflavin	8.0 μg.
Sodium acetate $3H_2O$	48 mg.	Thiamine HCl	1.6 μg.
Cysteine HCl	15 mg.	Pyridoxine HCl	6.4 μg.
Maltose	10 mg.	Pyridoxamine HCl	1.6 μg.
Difco agar	10 mg.	Pyridoxal HCl	1.6 μg.
$NaHCO_3$†	5 mg.	Ca pantothenate	3.2 μg.
Asparagine	2 mg.	Nicotinic acid	3.2 μg.
Ascorbic acid†	1,000 μg.	p-Aminobenzoic acid	1.6 μg.
Choline chloride	80 μg.	Biotin	0.8 μg.
Inositol	80 μg.	Folic acid	0.8 μg.
Ribose	40 μg.	Methylene blue (optional)	24.0 μg.
Adenine SO_4	40 μg.	Adjusted to *p*H 6.0, and Ringer's solution added to make:	8.0 ml.
Guanine HCl	40 μg.		
Xanthine	40 μg.	Human blood serum diluted with equal volume of Ringer's solution†	2.0 ml.
Uracil	40 μg.		
		Final volume	10.0 ml.

* To render the medium basal, serum is omitted.

† Added as sterile solutions after the medium was autoclaved (Sprince and Kupferberg).

xanthopterin and approximately 10 per cent human serum were employed, liver infusion was satisfactorily replaced. Sprince and Kupferberg[12] reported a medium which could be used as a starting point for the development of a chemically defined culture fluid for the sustained growth of *T. vaginalis*. A highly complex medium was devised with numerous growth factors included. (Table I.)

Unheated human serum is an essential constituent of the media devised for the cultivation of *T. vaginalis*. Sprince and Kupferberg, in an effort to determine the nature of the component(s) in human serum required by the protozoan, employed their highly complex medium. Human blood serum was separated by ether extraction into two fractions, both of which were found necessary for the sustained growth of *T. vaginalis* in trypticase serum basal (TSB) medium. The fractions were found to be (1) an ether-soluble fraction and (2) an aqueous ether-insoluble residue remaining after the extraction. The addition of both fractions to the basal culture fluid was essential to provide a complete nutrient medium since neither fraction alone would support growth. (Table II.)

At this point efforts were made to elucidate the nature of the essential material in the ether fractions as shown in tables III, IV, and V.

The addition of human serum albumin to the ether-soluble fraction supported limited growth of the organism. The results clearly show that human blood serum contains an unknown factor(s) which is required for optimum growth of *T. vaginalis*.

In an effort to determine the essential requirements of *T. vaginalis*, Kupferberg, et al[15] eliminated the vitamins, purines, and pyrimidines from the highly complex medium of Sprince and Kupferberg, and reduced the serum and trypticase content.

TABLE II

In vitro Cultivation of T. vaginalis *in Fractions Prepared from Human Blood Serum*

Ml. of diluted serum control* or diluted serum fraction* added to 8 ml. of Trypticase basal medium to give a total volume of 10 ml. per tube	Number of *T. vaginalis* per cu. mm. after 48 hours in each serial transfer†					
	First culture	Serial transfer 1	Serial transfer 2	Serial transfer 3	Serial transfer 4	Serial transfer 5
Control (2 ml. of diluted intact serum)	1,550	1,040	740	1,895	1,305	1,510
1.0 ml. diluted aqueous emulsion of ether extract + 1.0 ml. sterile Ringer's	0					
1.0 ml. diluted ether-insoluble phase + 1.0 ml. sterile Ringer's	990	540	0			
1.0 ml. diluted aqueous emulsion of ether extract + 1.0 ml. diluted ether-insoluble phase	1,080	685	1,205	2,335	1,755	1,145

* All samples of intact serum or serum fractions were diluted with an equal volume of Ringer's solution, as indicated in a preceding paragraph.

† Each value is the average of duplicate determinations (Sprince and Kupferberg).

TABLE III

Material in the Ether-soluble Phase Essential for the Sustained Growth of T. vaginalis

Fraction representing ether-soluble phase added*	Number of *T. vaginalis* per cu. mm. after 48 hours in each serial transfer†					
	First culture	Serial transfer 1	Serial transfer 2	Serial transfer 3	Serial transfer 4	Serial transfer 5
Control with intact serum	1,040	1,140	1,565	1,655	1,580	1,585
Aqueous ether-insoluble phase only	990	0				
Autoclaved aqueous ether extract + ether-insoluble phase	1,660	1,555	1,985	1,110	665	1,005
Dialysate of aqueous ether extract + ether-insoluble phase	2,075	1,340	1,895	1,695	1,600	1,640
Replacement mixture of pure compounds (replacing ether-soluble phase)	710	1,135	450	950	1,560	1,120

* All fractions equivalent to serum in concentration were diluted with an equal volume of Ringer's solution. One ml. of the diluted material was then assayed in test tubes containing 8.0 ml. of trypticase basal medium plus 1.0 ml. of diluted ether-insoluble phase.

† Each value is the average of duplicate determinations (Sprince and Kupferberg).

TABLE IV

Replacement Mixture of Pure Compounds for the Ether-Soluble Phase

Fat soluble compounds	μg. per 10 ml. of final medium
Lecethin	1000
Cholesterol	500
Oleic acid	500
Linoleic acid	500
Ergosterol	500
α-estradiol	50
α-tocopherol	5
β-carotene	1
Vitamin A	1

In the course of these studies a requirement for pantothenic acid and inorganic phosphate was demonstrated. The elimination of either of these substances resulted in the failure of these protozoans to multiply.

In table VI the nutritional requirements of *T. vaginalis* are tabulated.

The above study resulted in a simplified medium, Simplified Trypticase Serum (STS) medium, for the routine maintenance of cultures as well as for testing the antitrichomonas activity of compounds. This medium, to which Williams[16] added 250 units of penicillin and 1 mg. of streptomycin per ml. of medium, is employed routinely for the isolation of trichomonads from vaginal specimens. The composition and preparation of STS medium is shown in table VII.

In an attempt to replace trypticase in the TSB medium, Sprince, Gilmore, and Lowy[17] employed pancreatic extracts which gave good growth results. The active

TABLE V

Replacement of Ether-Insoluble Phase by Human Serum Albumin

Fraction representing ether-soluble phase added*	Number of *T. vaginalis* per cu. mm. after 48 hours in each serial transfer†					
	First culture	Serial transfer 1	Serial transfer 2	Serial transfer 3	Serial transfer 4	Serial transfer 5
Control with intact serum	1,180	1,170	1,170	915	1,565	1,655
Human serum albumin only	900	0				
Serum albumin + ether extract (aqueous emulsion)	355	460	615	450	393	335
Replacement mixture + serum albumin	570	0				

* All fractions equivalent to serum in concentration were diluted with an equal volume of Ringer's solution. One ml. of the diluted material was then assayed in test tubes containing 8.0 ml. of trypticase basal medium plus 1.0 ml. of diluted human serum albumin.

† Each value is the average of duplicate determinations (Sprince and Kupferberg).

TABLE VI

Nutritional Requirements of T. vaginalis

Ingredients per ml. final STS medium[14]		Known essential nutrients	Oxygen relationship	Optimum temp. (C.)	Optimum *p*H	Length (μ)
Trypticase (BBL)	20.0 mg.	Ca. Pant.	Anaerobic[8]	35–37[9]	5.8–6.0[5]	6.4–27.2[4]
Cysteine HCl	1.5 mg.	Inorganic				
(a) Maltose	1.0 mg.	phosphate[14]				
Agar (Bacto)	1.0 mg.					
(b) Serum (human)	0.05 ml.					
(c) Methylene blue	2.40 mg.					

General Remarks: (a) Glucose and polymers: maltose, soluble starch, glycogen and dextrose can be utilized.[10]

(b) Guinea pig, swine, horse, sheep and rabbit sera can also be employed.[11]

(c) Methylene blue used as an indicator and is optional.

(d) *T. vaginalis* produces CO_2 and lactic acid.[11]

factor in pancreatic extracts, called "s," is water-soluble, dialyzable, and thermostable.

These workers also found that Lipocaic (Lilly) possessed much greater activity than trypticase, and supported growth at 25 μg. /ml. whereas trypticase was not active at concentrations of 500 μg. /ml.

DETECTION OF *T. vaginalis* IN MALE AND FEMALE

Adequate treatment of any disease requires proper detection of the etiological agent. The methods employed in the detection of *T. vaginalis* are: (1) the hanging

TABLE VII

Simplified Trypticase Media[a]

	950 cc.
1. Maltose	1 Gm.
2. Bacto agar	1 Gm.
3. H_2O distilled	400 cc.
Heat in autoclave 10 lbs. for 10 minutes to dissolve agar. Filter through coarse paper (Reeve-Angel).	
4. Trypticase (BBL)	20 Gm.
5. Cysteine HCl	1.5 Gm.
6. 0.5% Methylene blue	0.48 cc.
7. Add distilled H_2O to make	600 cc.
Adjust to *p*H 6.0 with 5N NaOH. Make up to volume with distilled water. Tube in 9.5 cc. amounts.[a] Autoclave 15 lbs. for 15 minutes and cool to room temperature. Add 0.5 cc. sterile serum (100%) which has been adjusted to *p*H 6.0.	

[a] Where the testing of compounds is contemplated, the final volume may be reduced to allow for the addition of the material to be assayed.

drop or wet smear technique, (2) staining techniques, and (3) the use of cultures.

It has been shown by Kean and Day[18] that the use of stained preparations offers no advantages over the wet-smear technique. On the contrary, the laborious nature of this method does not make it a desirable tool for either office or laboratory use in the detection of *T. vaginalis*. Culture techniques have been used these past years with excellent results, particularly when evaluating therapeutics as potential trichomonacides.

Johnson, Kupferberg, and Hartman[19] have shown that infection in the monkey is characterized by abrupt fluctuations in the number of protozoa, with peak populations of brief duration restricted to the period of approximately a week before and a week after the menses (fig. 1).

In the mid-cycle the parasites are often difficult to demonstrate by wet smear technique for prolonged periods, even when 100 fields on each slide were examined. A study by Williams on these experimentally infected monkeys soon revealed that many so-called negatives by the wet slide technique were positive when culture methods were employed. Since then Kean and Day confirmed this observation in human beings, and further emphasize the unreliability of the microscopic examination of the wet smear preparation for evaluating therapeutic effectiveness in trichomoniasis. While the wet smear technique is unreliable in evaluating a therapeutic, its use is essential for the proper diagnosis of vaginal trichomoniasis in the usual office practice where incubators and culture media are not readily available.

T. vaginalis IN THE MALE

In 1894 there appeared, almost simultaneously, reports by Marchand, Miura, and Dock who found trichomonads in the urinary tracts of male patients. Allison[20] re-emphasized this entire problem. He demonstrated *T. vaginalis* in 15 per cent of the male patients examined. These figures were obtained by employing the wet-smear technique. Recently a study by Guttmacher and Perl,[21] who employed culture methods, revealed that of 65 men whose wives had trichomoniasis, 30 men, or approximately 45 per cent, harbored the organism in semen samples submitted for evaluation. These investigators found that cultures of urine samples from this same group of men gave only a fraction of positive cultures as compared to the results of the cultures of semen. It soon became apparent that the use of semen samples was the preferred method for the detection of *T. vaginalis* in the male. It is therefore obvious that successful control of this disease must take into account the fact that a large percentage of the husbands of infected women harbor the organism. Furthermore, in therapeutic evaluation, the male as well as the female must be examined by culture methods. Attempts to find trichomonads in sperm by the wet-smear technique is totally unreliable because of the motility of the sperm.

WET SMEAR TECHNIQUE

For office use, a specimen is taken from the posterior fornix of the vagina with a cotton-tipped applicator and rotated in a test tube containing 1 to 2 ml. of Ringer's

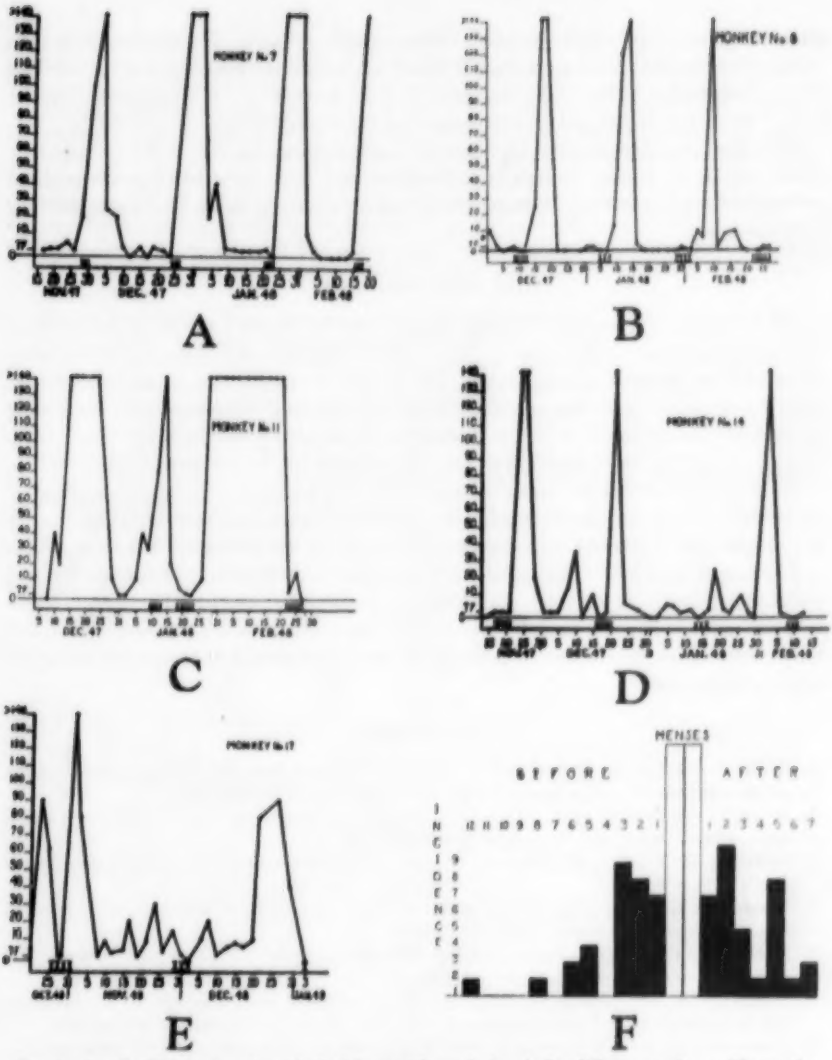

FIG. 1. A to E—Fluctuations in vaginal trichomonad populations in five different monkeys. The number of trichomonads per low-power field is shown on the vertical axis. TF = less than one trichomonad per low-power field. X = days on which menstrual bleeding was observed. In C the first menstrual period, December 1 to 4, is not shown. Attention is called to the abnormally short cycle in mid January, 1948, followed by a prolonged elevation in parasite population. This was the only observed case of this kind.

F—Summary of observed population maxima in nineteen infected monkeys. The number of times that a peak in population was reached is plotted on the vertical axis. The days before or after the menses on which such peaks were reached are plotted on the horizontal axis. It is clear that such maxima are reached most frequently in the period around menstruation. On the other hand, it is shown that in all infected monkeys population maxima were reached only twice on the twelfth day and twice on the eighth day prior to menstruation. (Johnson, Kupferberg and Hartman.)

solution, physiologic saline, or some other suitable diluent. The applicator is then rolled over the surface of a glass slide which is examined under the low power lens of the microscope. The organism can be readily observed as a colorless, motile form. No other flagellated protozoa exist in the human vagina.

No special precautions need be taken in examining the slides. It is not necessary to employ warm slides, though it is recommended that the diluent not be chilled and the slide be examined at room temperature. Chilling slows down the motility of *T. vaginalis*.

CULTURE TECHNIQUE

The technique employed in making a diagnosis is to obtain a sample of the material in which *T. vaginalis* is suspected. This is placed in a tube of STS medium containing antibiotics as previously mentioned. The culture is then stored in an incubator at 37 C. for a period of 48 hours. The culture is examined microscopically on a slide under low power, and if negative, stored in the incubator for another 2 to 3 days. If again negative, the culture may then be discarded. In evaluating therapeutics, it has been our custom to culture a vaginal or semen sample at least one week after all therapy has been discontinued. If negative, a second culture is taken two to four weeks later. Should this culture be negative by the above criteria, the patient is discharged as cured. The need for prolonged microscopic examination by wet smear technique is unnecessary where culture methods are employed.

It is apparent that in experimental studies of trichomoniasis the uses of cultures are essential if one is to speak of *parasitologic cures* as compared to temporary asymptomatic clinical effects.

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Trichomonas vaginalis Vaginitis

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Donne, in 1837, was the first to note the organism, *Trichomonas vaginalis*, in vaginal secretions, and his accurate description of it, and of the vaginitis which accompanies its presence, has withstood the test of time. For 80 years most of the European gynecologists considered it a harmless parasite, and until 30 years ago most American gynecologists were unaware of its existence.

From 1896 to 1929 there was only an occasional report in the American literature. Since 1929 there has been an increasing number of papers by many investigators. An enormous amount of research, both basic and clinical, has been carried out in innumerable clinics throughout the world. Each report presents a different theory and a different treatment. Most of the papers present a "new treatment" with great enthusiasm, often with "90 per cent plus cure." It is disillusioning to read a few years later that this wonderful treatment has been discarded by the author for another, and another still again. It is over a hundred years since Donne's original observations; yet despite all this intensive investigation, accurate knowledge of the portal of entry, the mode of transmission, or the specific treatment still eludes us.

ETIOLOGY AND INCIDENCE

It took a long time for investigators to come to the present general agreement that this trichomonad is pathogenic. In the 1930's a popular theory was that infestation of the vagina was transmitted from a rectal infection. We now know that the rectal and vaginal organisms are different forms of the flagellate, and that there is no cyst stage. In most of the cases seen of vaginal infestation, the rectum is free of the rectal form. In the occasional case seen with rectal infestation, the vagina is usually free of it. I do not believe there is any correlation, nor that the rectum is responsible for vaginal infestation. Although it is found at all social levels and in the most meticulously clean women, the incidence becomes progressively higher as the social scale becomes lower. In the uppermost socioeconomic level, the incidence in my series was 9 per cent in 5000 consecutive gynecologic cases. Of these, the age range was 15 to 65 years. Twelve per cent were postmenopausal, and 9 per cent were virgins; 5 per cent were symptom-free, and 3 per cent had no abnormal clinical findings. (I have never seen a case before the onset of menses in this upper social level.) The incidence in the lowest socioeconomic level increases progressively as we go down the scale to 65 per cent. Even in this group only a handful were prepubertal.

The cuboidal epithelium of the male's genitourinary tract seems to be relatively immune to these flagellates. There has been a rare report of an occasional acute urethritis or cystitis in a male. Men can be carriers and entirely unaware of the fact. Undoubtedly this is responsible for some infections and reinfections in women.

TABLE I

Differential Diagnosis of Common Forms of Vaginitis

Trichomonas	*Gonococcus*	Fungus	Endocrine
	Etiology		
Flagellate, easily found in fresh wet smear	Gram-negative, biscuit-shaped diplococci, found in stained smear and culture	Found in wet smear diluted with 10% sodium hydroxide or in gram-negative stained smear	Metabolic disturbance of vaginal mucosa due to estrogen deficiency
	Age of Incidence		
After puberty	Before puberty	Any age, greatest incidence during pregnancy	Postmenopausal
	Clinical Findings		
Acute vulvitis and vaginitis, multiple punctate spots—"strawberry vagina"—foamy charge with characteristic odor	Acute vaginitis of immature vagina—adult vaginal mucosa resistant to gonococcus	Acute vulvitis and diffuse vaginitis with appearance of raw beef. Punctate red spots absent	Diffuse vaginitis. If acute, may present picture of "strawberry vagina." Discharge not foamy and less malodorous than trichomonas
	Urethritis and Skenitis		
Present—urethral discharge scant and thin	Present—urethral discharge more purulent	Not involved	Not involved
	Cervical Erosions		
Often present—concentric or eccentric	Child's cervix not as frequently involved	Coexisting, if present	Coexisting, if present
	Endocervicitis		
Endocervix not involved. Canal secretions clean	In child, endocervix not involved—in adult usually involved with thick, purulent discharge	Not involved	Not involved
This is one of the important differential points between these two infections.			
	Symptomatology Leukorrhea		
Thin, foamy, amount varies, with characteristic disagreeable odor	Thick, purulent, usually profuse	Thick, amount scant, characteristic—resembling bits of cottage cheese	Usually scant—occasionally profuse and purulent
	Itching		
Prominent symptom	Insignificant	Marked	Varies
	Burning		
Varies	Little or none	Prominent symptom	Prominent symptom
	Dyspareunia		
Marked		Marked	Marked
	Dysuria		
Present	Varies	Varies	Varies
	Response to Therapy		
No specific treatment; no response to penicillin	Penicillin specific	Gentian violet specific. Gentersal (Ortho) is an excellent vehicle for this therapy	Estrogen intravaginally specific

It is usually impossible to demonstrate their presence in the male except with careful culture of their semen and of the prostatic secretion obtained by massage.

DIAGNOSIS

The diagnosis is easily made and quickly verified; yet there is still a high percentage of error, because the organism is too often overlooked, or not looked for.

Symptoms: The symptoms are so characteristic that the diagnosis can usually be made on the history. The most common symptom is an irritating leukorrhea with a disagreeable odor frequently accompanied by itching, especially at the onset. Accompanying dysuria may be due to burning of the chafed skin, or to an irritation of the external urethra often found in the acute stage. Dyspareunia is a frequent symptom.

Clinical Findings: Unless the patient has been douching frequently, physical examination will show an acute vulvitis with a scant, foamy discharge between the labia. There may be a dermatitis of the vulvoperineal area and the contiguous surfaces of the upper thighs. The vagina is inflamed, with many punctate hemorrhagic spots giving the characteristic appearance of a "strawberry vagina." The mucosa of the supravaginal portion of the cervix is red, with similar punctate red spots. Frequently there is a cervical erosion of varying size or an eccentric erosion of the portio away from the external os. This is the only type of infection in which I have seen this peculiar type of erosion. The vault of the vagina contains varying amounts of discharge, white or yellow, thin in consistency with minute air bubbles causing a foamy appearance. The urethral glands and Skene's ducts are often involved. A few fine condylomata are present in a small percentage of cases. Rarely, there is an incredibly luxuriant growth of large condylomata.

The endocervical mucosa is not affected and is apparently as immune as the male cuboidal epithelium. This is one of the important differentiations between trichomoniasis and gonorrhea. In trichomoniasis the canal is clean and not involved. For example, while doing Hühner tests, I have found no trichomonads in the cervical canal above the level of the external os, in cases where the cervix was bathed in a seminal pool swarming with trichomonads. In gonorrhea, however, the canal is usually involved, presenting a characteristic, purulent endocervicitis.

Microscopic Technique and Findings: The diagnosis can be verified quickly by examination of a fresh wet smear. Comparison between search for trichomonads by examination of the fresh wet drop, the stained smear, and the cultural method shows that the wet smear is as accurate, much simpler, and will verify the diagnosis on the spot.

A dry, gloved finger is inserted. Using a sweeping motion around the vault of the vagina, some of the vaginal secretion is withdrawn. A drop of this discharge is placed on a clean glass slide. Two to three drops of normal saline solution are immediately added and stirred in with the corner of a cover slip, which is then placed over the fluid. The slide is examined immediately under the high-power lens.

The picture is typical: a large number of pus cells, few or no epithelial cells, and in every field are numbers of trichomonads. I shall not describe the organism, as it

is recognized only by its characteristic motion, and one glance at the living organism will convey more than pages of description. The live trichomonad is in constant motion, and when free from debris, can move rapidly. When caught under a group of cells, it will agitate the entire clump in a rapid, to-and-fro, whiplike motion. When dead, it appears round and cannot be differentiated from the pus cells. It is therefore not recognizable unless alive and free to move. In order to recognize the organisms in a stained smear, special staining techniques have to be used. The Papanicoloau stain demonstrates the organism well. For this reason and because in cases of leukorrhea the fresh secretion is not routinely examined, trichomoniasis is frequently not diagnosed or is erroneously diagnosed as some other infection. The most serious error is when it is mistaken for gonorrhea.

The clinical history and findings may simulate gonorrhea closely. In *Trichomonas vaginalis* vaginitis, the stained smear shows large numbers of pus cells with few other bacteria. A diplostreptococcus is a frequent accompanying organism to the *Trichomonas*, and in the stained smear, this diplococcus may be misinterpreted as the gonococcus. This error was commonly made three and two decades ago. With diminishing incidence of gonorrhea, and the general spread of knowledge about the *Trichomonas*, this error in diagnosis has been reduced radically but it still occurs. Smears should nevertheless be taken, and a careful search for the gonococci made, for both infections may be present at the same time. Table I summarizes the more important points in the differential diagnosis of the common forms of vaginitis.

In *T. vaginalis* infestation, the organism may not be recognized under these conditions:

1. If a douche or other medication has been used within 7 to 14 days before examination.
2. If soap or glycerin or other lubricant damaging to the organism is present on the gloved finger.
3. If the slide is allowed to dry, since the organisms are killed rapidly by drying.
4. If the smear is so thick that the organism does not have room to move around freely and is obscured by thick clumps of pus cells. Since the organism is only recognized by its motion, there must be sufficient dilution with normal saline to give a clear picture, with ample space between cells for the organism to move about.
5. If the use of a cover slip or the high-power lens is omitted.
6. If the saline is not of the proper strength. It must be normal physiologic solution.
7. If the microscope is too close to open windows, the organisms may be chilled and do not move. Although it is not necessary to use warmed saline or a warm stage, the saline and room should be at about 72 F. The microscope light, placed directly under the stage, keeps the temperature favorable for prolonged observation.

Trichomonas may be erroneously reported to be present if an inexperienced observer looks at the slide while the fluid is still in motion and interprets pus cells or other

cells moving with the stream as trichomonads. Active sperm may whip a leucocyte around in the motion characteristic of *Trichomonas*, and lead to error.

Avoidance of the above-mentioned pitfalls will eliminate many errors in diagnosis. Since blood apparently gives the organisms their greatest impetus to growth, the best time for examination is shortly after a menstrual period, with no douche or treatment since the onset of the period. If all the above details are kept in mind, even the novice will be able to make a correct diagnosis with assurance in most cases. It takes more experience to recognize the organism in chronic cases than in acute cases. If the organism has little vitality, it usually takes on a symmetrical round shape, resembling a pus cell, the movement may be minimal or the organism may be stationary with only the flagella whipping around in a slow and lazy motion. Taking the time to examine the fields slowly and with care, cutting the light down, will help to recognize the movement of the flagella. There has to be definite recognition of this movement, and several trichomonads should be found before the diagnosis is made.

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Vaginal Trichomoniasis Treated with a Preparation Containing Tyrothricin

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Despite the enthusiasm of many investigators for their particular form of therapy for treatment of *Trichomonas vaginalis* vaginitis, the search for more effective and less toxic preparations still continues. The very multiplicity of therapeutic procedures that have been recommended in itself reveals a lack of acceptance of any one as an effective means of treatment of this prevalent and, at times, serious infection. The complex nature of the *Trichomonas* organism, as considered in another paper in this Symposium by Kupferberger[1] may afford one explanation for the difficulties that at times have been encountered in attempts to control infection due to this protozoon. When its habitat is readily accessible as in the vaginal tract the problem would appear to be much simpler than in the male where they are not so readily accessible to trichomonicidal agents. However, whether due to the complexity of their life cycle or other characteristics, eradication of trichomonads from the vagina has not been uniformly accomplished by a variety of types of therapy ranging from those whose sole purpose was to alter the vaginal *p*H to the broad spectrum antibiotics and those possessing specific protozoocidal activity.

The rationale of attempts to restore the vaginal reaction to its so-called normal, acid *p*H is based on the concept that *T. vaginalis* is unable to survive in such an acid medium. Hence, many have used vinegar douches. Yet the ability of a douche to maintain a persistently acid *p*H would appear to be highly questionable in view of the short period of contact of the acidic douche with the vaginal secretions. Moreover, it has been pointed out that acid coagulates the vaginal mucus thus tending to coat the flagellates with an impervious pseudo-membrane which effectively blocks access to the organisms of any trichomonicidal agents.[2] These objections have been largely overcome by use of carbohydrates such as β-lactose which can be fermented *in situ* by the vaginal flora.

Other agents that have been used in the past include the iodinated quinoline derivatives, various forms of pentavalent arsenic, and silver and mercurial salts.

With the advent of the "broad-spectrum" antibiotics, it was hoped that a more specific type of trichomonicidal agent might become available and would prove more effective in the treatment of vaginal trichomoniasis. While it is true that in vitro studies demonstrated a high degree of trichomonicidal activity, their clinical use was all too frequently associated with certain undesirable side effects attributed to disturbances in the symbiotic relationships existing in the microbial flora of the vaginal tract. As a result, the broad spectrum antibiotics too often substituted one disturbing infection for an equally serious or more recalcitrant one. Thus, following

their use, one would note an increase in *Candida*, frequently heralding the onset of an almost intractable monilial vaginitis.

As is true with many problems in clinical medicine, the selection of therapeutic agents for the effective treatment of a specific infection is often the result of a series of preliminary in vitro studies. This has been particularly the case in trichomoniasis inasmuch as in vitro techniques reveal the quantitative degree of sensitivity of the protozoon to different agents. Thus, Weinman reported in 1943 on the effect of gramicidin and tyrocidin upon the trichomonads both in vitro and in vivo.[3] It appeared from his data that tyrocidin is an effective agent in controlling the trichomonad organism in vitro. In addition, he noted that when 0.5 mg. of tyrothricin was instilled into the vagina, the antibiotic appeared to be an effective and efficient therapeutic agent. However, follow-up studies revealed a very high percentage of post-treatment relapses and the trichomonads then isolated were usually noted to be uninhibited in vitro by the same level of tyrothricin which had been previously effective. Later Greenblatt and his co-workers[4] and Shaw et al[5] were able to confirm the effectiveness of tyrothricin with both in vitro and in vivo studies. Thus, Greenblatt and West[6] demonstrated that in vitro tyrothricin was by far the most potent trichomonicidal of all the antibiotics tested by them. Both these groups of workers reported effective control of *Trichomonas* vaginitis with infrequent relapse could be achieved by administration of adequate doses of tyrothricin. Greenblatt and West concluded that tyrothricin not only afforded a degree of clinical effectiveness unsurpassed by other antibiotics, but also that its use was complicated by significantly fewer side reactions. Weinman's observations, however, were not confirmed by Johnson who obtained rather indifferent results when tyrothricin was administered in the form of a neutral or acid suppository.[7]

Another agent frequently recommended for the effective therapy of trichomoniasis is phenylmercuric acetate, a time-tested remedy frequently employed by gynecologists. Biskind noted, that when 2 mg. of phenylmercuric acetate were administered in the form of a jelly, he observed marked improvement in both objective and subjective findings in his patients.[8] Phenylmercuric acetate has also been employed together with a wetting agent in an attempt to permit a more intimate contact between the protozoocidal agent and the organism itself. This is particularly important for trichomonads in whom there has been described a mucoid-like membrane surrounding the organism. This may well be relatively impervious to most of the agents used in treatment of trichomoniasis. The use of a wetting agent, when combined with selected therapeutic agent should permit a greater contact between the therapeutic agent and the protozoa. A commonly used wetting agent which has been recommended for this purpose is sodium lauryl sulfate. This substance by virtue of its detergent action markedly reduces surface tension. As a result, it causes preparations in which it is contained to "spread" and cling, thus encouraging a more intimate and prolonged contact between the accompanying active ingredients and the infecting microorganism. Such a spreading and clinging action would appear to be particularly important in the vagina whose many crypts and mucosal folds would otherwise provide ideal sites in which the protozoa might escape contact with the trichomonicidal agents.

Many of these principles have been utilized to formulate a vaginal suppository consisting of a combination of tyrothricin, phenylmercuric acetate, sodium lauryl sulfate, β-lactose and water-soluble chlorophyll.* This last was included primarily to provide its antipruritic, wound-healing, and deodorant properties,[9] β-lactose, as discussed above, provides a favorable medium for the growth of Döderlein's bacilli, thus favoring maintenance of vaginal acid *p*H. At the same time, since it is not fermentable by *Monilia*, it does not favor growth of the latter. Certainly the combination of tyrothricin and phenylmercuric acetate could be expected to provide more effective results than either one alone. This combination of ingredients is somewhat comparable to that suggested by Shaw et al,[6] except in the concentration of tyrothricin, which is considerably greater, being ten to twenty times as much as Shaw has used.

A preliminary study of the use of this combination has already been reported by us.[10] In this study, we first investigated the effect of variation of tyrothricin content as well as of the dosage schedule. It was found that very satisfactory results were obtained by the administration of one suppository per day, containing 5 mg. of tyrothricin. An increase of the number of suppositories used per day or an increase in the tyrothricin content from 5 mg. to 10 mg. per suppository failed to enhance the therapeutic efficacy. On the other hand, whereas use of one suppository, containing 5 mg. per day was found to be attended with little or no side effects, the other therapeutic regimens were noted to be associated with an increasing number and severity of undesirable side effects. In brief, these consisted of vaginal burning, particularly in the labia, vaginal lesions varying from denudation to excoriation, urinary frequency, and an objectionable green discharge.

In this preliminary publication, we emphasized that the reported results must be regarded as provisional in nature. In the first place, it was believed that too few patients had been included under each of the four categories of treatment. Secondly, in view of the short period of follow-up observation then permitted, it was considered essential to defer any final conclusions until we could undertake a somewhat more extensive study of the effects of use of this combination. This present report is therefore concerned with a somewhat larger scale study of the effects of administration of one suppository per day, each containing 5 mg. of tyrothricin.

METHODS

The procedures used are essentially similar to those described in our preliminary report.[10] Following diagnosis, which was always confirmed by demonstration of typically motile *T. vaginalis* in a fresh hanging drop, the patient was instructed to insert one suppository per day, containing 5 mg. tyrothricin, high into the vagina, preferably at night upon retiring. This was continued for 10 consecutive days when this first phase of treatment was discontinued. Shortly thereafter, the patient was seen again and another hanging drop examined to note whether trichomonads were

* Furnished under the trade name, Colpotab, by the Purdue Frederick Co., New York City. Each Colpotab vaginal insert contains: tyrothricin, 5 mg.; phenylmercuric acetate, 3 mg.; sodium lauryl sulfate, 7.5 mg.; β-lactose, 1.17 Gm., and water-soluble chlorophyll, 10 mg.

still present. Regardless of the findings, patients were instructed to reinstitute treatment, one suppository per night, beginning with the onset of the subsequent menses and to continue to do so for five consecutive nights and then to discontinue treatment once more. Again, they were re-examined, both clinically and with a hanging drop. A similar procedure was again instituted during the period of the next menstrual flow, at the end of which time treatment was considered completed. If, then, in the absence of any clinical evidence of trichomoniasis, the hanging drop proved negative, the patient was considered cured. At no times were cultures used to confirm this impression. As is noted later, since douches were strictly interdicted, their use could not obscure the results of examination.

It is believed that a therapeutic agent cannot be properly evaluated if other procedures, which likewise exert an appreciable effect on the course of the disease, are used concomitantly with the agent under study. For this reason, two procedures frequently used as adjunctive measures in the treatment of vaginal trichomoniasis were not employed. All patients were instructed not to use any type douche during the entire course of treatment. Furthermore no measures were used to interfere with sexual contact. Accordingly, it is felt that the results of this study provide a valid index of the degree of effectiveness of Colpotab, *per se*, in the treatment of trichomoniasis.

The degree of effectiveness was computed in terms of a therapeutic index which considered both the effect on the course of the disease itself as well as the presence of complications in the form of undesirable side reactions. The criteria for evluation of the therapeutic index follow:

"A": No trichomonads after treatment; complete clinical improvement; no side effects.

"B": Trichomonads still present after treatment; improvement in all clinical symptoms.

"C": Trichomonads still present after treatment; no or little improvement in symptoms, indicating complete failure.

RESULTS

The patients included in this study ranged in age from 22 to 50 years, the great majority being in the third and fourth decades of life. Only 1 patient had attained her menopause. In addition to those reported in our preliminary publication, we are now able to describe the effects of one suppository per day, containing 5 mg. tyrothricin, in 36 other patients. The results of treatment are summarized in Table I.

Of these 36 patients, 15 failed to return for further observation after completion of the initial, first 10-day phase of treatment. At the end of that time, 3 of these could be considered as clinically cured, and hanging drops were negative. Five others exhibited significant clinical improvement but must be considered as treatment failures since hanging drops still revealed trichomonads. The other 7 of these 15 were classified as outright treatment failures.

Nine patients completed both the first phase of treatment as described above as

TABLE I

Response of Patients to Treatment for Trichomoniasis

Patient	Age	Therapeutic Index After Initial Phase of Treatment	Duration of Subsequent Therapy	Therapeutic Index at End of Treatment	Remarks
BH	50	A	1 cycle	A	
MN	41	C	None	C	Patient did not return
FQ	24	B	None	B	Patient did not return
BG	29	B	2 cycles	A	
MS	32	C	None	C	Patient did not return
JV	33	A	1 cycle	A	Patient did not return
MS	30	C	None	C	Patient refused further treatment
CR	22	A	None	A	Patient did not return
MD		A	2 cycles	A	
SC	26	A	1 cycle	A	Patient did not return
OT	33	A	1 cycle	A	Patient did not return
ETS		B	None	B	Patient did not return
SC	38	B	2 cycles	B	Positive hanging drop obtained after second menses; marked clinical improvement
MD	31	A	1 cycle	A	Patient did not return
LE	26	C	None	C	Patient did not return
AR	29	A	1 cycle	A	Patient did not return
DL	27	B	None	B	Patient did not return
GD		A	None	A	Patient did not return
SK	39	B	1 cycle	A	Hanging drop negative
RW	22	B	None	B	Patient did not return
ER	32	A	None	A	Patient did not return
NT	27	C	None	C	Trichomonads disappeared with use of vinegar
CG	38	A	1 cycle	A	Patient did not return
SM	35	B	None	B	Patient did not return
CG	40	A	1 cycle	A	Patient did not return
FN	31	A	3 cycles	A	Patient controlled as long as she uses suppositories during each menses
SF	29	A	5 cycles	A	
DH	39	B	2 cycles	A	Patient controlled as long as she uses suppositories during menses
ES	28	A	2 cycles	A	No recurrence in 9 months
MG	25	A	2 cycles	A	No recurrence in 9 months
FR	28	C	3 cycles	B	Discharge diminished, trichomonads decreased but still present
NG	24	C	None	C	Patient refused further treatment
FP	38	B	2 cycles	B	Discharge diminished but few trichomonads still persist
SZ	41	A	3 cycles	A	No recurrence in 5 months
PT	26	B	2 cycles	A	No recurrence in 3 months
SK	28	C	None	C	Changed to arsenical with good results

Therapeutic Index evaluated as in text.

well as that during the next menses. Of these, all 9 exhibited all clinical evidences of cure as well as negative hanging drops.

Twelve patients completed the entire prescribed course of treatment. Of these, 9 exhibited all evidences of clinical cure as well as absence of trichomonads in the hanging drop. Three others were significantly improved but trichomonads were still present.

A summary of the evaluation of treatment, according to the length of time treated, is presented in Table II. This demonstrates that of the total of 36, hanging drops indicated that trichomonads had been eradicated from 21, or 58 per cent. An additional 23 per cent demonstrated clinical improvement. This over-all rate, as noted above, includes the results obtained in patients who completed only the initial ten day phase of the entire recommended course of treatment. If these latter patients are temporarily excluded, of the 21 patients who completed treatment during at least one subsequent menstrual period, 18 fulfilled the clinical and laboratory criteria for successful treatment of trichomoniasis. The cause for the disparity in the degree of response of the two groups of patients to medication is not immediately apparent at the present time.

Inspection of Table I reveals that, in patients in whom further follow-up was possible, recurrences were not noted for periods up to nine months after treatment (2 cases). In a few others who, after treatment, were completely free of pruritus and vaginal discharge after an intervening two or three menstrual periods, pruritis and discharge were again noted. These patients undertook self-treatment whereby they would insert the vaginal suppositories during their menses and, by so doing, found they remained completely free of symptoms and complaints. Re-examination of these patients at this time revealed that they are free from disease.

One of the more readily apparent effects of treatment was the very rapid disappearance of symptoms. Even patients who, in addition to their trichomoniasis suffered from almost every kind of vaginal infection, commented that they did become relatively free of pruritis and the objectionable vaginal discharge. It is assumed that credit for much of this symptomatic relief is due to the soothing and anti-pruritic properties of the water-soluble chlorophyll in the medication.

Of particular interest is the fact that there was no evidence of disturbance in the vaginal flora as the result of therapy. Not a single case of vaginal moniliasis was observed after treatment. Similar results certainly cannot be anticipated with other antibiotics.

DISCUSSION

In many respects, the present results confirm and extend those reported in our preliminary study. Several of these are worthy of comment. In the first place, reference to table II emphasizes the necessity for completion of the entire prescribed course of treatment. Obviously, a lower incidence of cure-rate was obtained in those patients who received the benefit of only the first 10-day phase of treatment. Secondly, the fact that the use of one suppository per day, containing 5 mg. tyrothricin, is attended by no apparent side reactions is adequately confirmed. Not a

TABLE II

Effect of Duration of Treatment on Therapeutic Index

Duration of treatment	Therapeutic index		
	A	B	C
Initial 10-day phase of treatment	3	5	7
One or more cycles of treatment	18	3	
Total treated	21	8	7

Therapeutic Index defined in text. For description of phases comprising duration of treatment, see "Methods" in text.

single patient of the 36 treated with this regimen exhibited any untoward reactions to therapy, in sharp contrast to what had been observed in patients placed on regimens providing larger amounts of tyrothricin per day.

The over-all "cure-rates" reported here are lower than those described in our preliminary report but, at that time, we emphasized that longer periods of follow-up observation were required to validate the then tentative conclusions.

According to both Greenblatt and West[6] and Barfield,[11] both of whom have undertaken a series of critical examinations of the effectiveness of various advocated treatments for trichomoniasis, severe suspicion must be cast on reports which describe excessively favorable results in the treatment of trichomoniasis. According to both of these, in their hands no treatment has proved more effective than approximately 70 per cent. Unfortunately, the few agents which provide success to this degree are frequently complicated by undesirable side reactions. Colpotab, on the other hand, provides therapeutic effectiveness and for all practical purposes is almost totally devoid of undesirable side effects.

SUMMARY AND CONCLUSIONS

1. A group of patients with vaginal trichomoniasis was treated with a vaginal suppository containing 5 mg. tyrothricin, 3 mg. phenylmercuric acetate, 10 mg. water-soluble chlorophyll, 7.5 mg. sodium lauryl sulfate, and 1.17 Gm. β-lactose. Recommended schedule of treatment was described, consisting of the insertion of one suppository per day during the prescribed period, comprising segments of three consecutive menstrual cycles.

2. The therapeutic effectiveness of such treatment with this combination, called Colpotab, was considered satisfactory. These results were obtained without recourse to any adjunctive hygienic measures as are commonly utilized for trichomoniasis.

3. In addition to the eradication of trichomonads from the vaginal tract, treatment with Colpotab was characterized by a prompt subsidence of all complaints and symptoms.

4. In contrast to the broad spectrum antibiotics, treatment with Colpotab produced no evidences of disturbances in the vaginal flora and not a single case of moniliasis complicated its use.

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EDITORIAL SURVEY

Viral Hepatitis

Viral hepatitis is a common contagious disease which reaches the proportion of minor epidemics in some regions of the United States. How serious the problem is can be seen in the fact that more than 2000 articles on the disease have appeared in medical publications during the last five years.

The disease has been known for thousands of years. Hippocrates mentions it, and it appears in letters written by Zacharias to Boniface (eighth century) in which he advises persons with jaundice to be isolated in order to restrict contagion. The armies of the Napoleonic Wars, the Civil War, and both World Wars all suffered heavily from "infectious jaundice," or "catarrhal jaundice," as the entity has been variously called. During World War II there were more than 50,000 cases of jaundice following injection of yellow fever vaccine containing human serum. It was subsequently discovered that yellow fever had nothing to do with the outbreak, the fault lay in the serum.

CAUSATIVE AGENTS

Viral hepatitis is generally attributed to two types of virus: Virus A which causes infectious hepatitis (IH) and Virus B responsible for serum hepatitis (SH).* Having said that, we are not much further advanced, inasmuch as neither of the viruses has so far been isolated, it is impossible to cultivate them in vitro, and no other animal besides man seems inclined to contract the disease. We do know that both miscreants can pass through filters capable of removing bacteria, and there is evidence that Virus B measures 26 microns or less. The latter also appears to possess astonishing resistance to heat or ultraviolet radiation sufficiently intense to inactivate most other viruses. That is practically all we know about these elusive organisms.

CLINICAL PICTURE

The clinical picture of infectious hepatitis is quite confusing. In adults, the onset of this disease can be sudden or it can be insidious. The first phase can last a day, a week (the usual time), or three weeks. It can bring headache, lassitude, generalized aches, and pains, backache, nausea, loss of appetite, vomiting, abdominal distress, and sometimes a dragging sensation in the right upper quadrant. Many persons also suffer from fever, often accompanied by a chilly sensation. From these symptoms, one suspects that many of the so-called "Virus X" or "forty-eight hour virus" attacks are nothing else but fairly mild attacks of infectious hepatitis. The incuba-

* This entity formerly boasted such names as homologous serum hepatitis, transfusion jaundice, post-vaccinal jaundice, postinoculation jaundice, and delayed arsenotherapy jaundice. As it is, "serum hepatitis" is itself a poor term, as both types of virus can be transmitted by parenteral injection.

tion period is said to be between 10 and 50 days, which is another way of saying that we have no real idea how incubation proceeds.

That is the preicteric stage beyond which a proportion of patients never pass. When jaundice does declare itself, it is accompanied by abdominal discomfort, a "heavy" sensation in the region of the liver, severe anorexia, nausea, and often vomiting. This miserable condition lasts from one to ten weeks, averaging about four weeks for the younger adult. The liver is usually enlarged and tender and in some cases the spleen is also palpable and tender. The skin, of course, takes on its distressingly yellow hue, and in some cases spider angiomata add their share to the patient's misery. When the jaundice reaches its highest intensity, there is usually subjective improvement and the patient's appetite returns. Convalescence is then quite rapid, although some persons continue to show a low grade jaundice for several months. Weight loss is a common finding.

The clinical picture in children resembles that of adults except that it is generally much milder and is rarely accompanied by jaundice. The onset is often abrupt, with headache, and fever as high as 102 F. Abdominal pain and vomiting are frequent symptoms. On the other hand, infectious hepatitis can creep on insidiously, the only symptoms being the common upper respiratory complaints of children, with congested nasopharyngeal membranes and enlarged posterior cervical lymph nodes.

The course of hepatitis caused by Virus B is similar to the one just described, including as it does both the icteric and nonicteric forms. The incubation period of Virus B is said to be between 60 and 140 days, which from an epidemiologic or preventive standpoint is a fairly worthless piece of knowledge. The onset of serum hepatitis is generally insidious and there is rarely any fever. Convalescence usually lasts much longer than in the A type of infection. Recently a form of viral hepatitis has been noted in the newborn and young infants, believed to be transmitted via the placenta.

LABORATORY DIAGNOSIS

As it is impossible to isolate the viruses of both types, the physician must content himself with a series of laboratory procedures, most of them costly and time-consuming, to determine the existence and extent of damage to the liver. The general value of these tests is to (a) help substantiate a diagnosis; (b) screen early cases during the nonicteric or preicteric stages; (c) aid in managing the patient once the illness is established.

Of the various tests, the bromsulfalein (B.S.P.) excretion test is useful, although it should not be used on icteric patients. A sensitive urine test is the one for urobilinogen excretion. Early in the course of hepatitis, there is an accumulation of urobilinogen in the blood owing to the inability of the damaged liver cells to excrete the normal amount absorbed from the intestine. Increased amounts of urobilinogen in the urine can thus be a sign of the onset of hepatitis, with the added advantage that the test is economical and easy to perform.

If there is any doubt about the original diagnosis, cephalin flocculation and thymol turbidity tests may be performed. They are positive in at least 80 per cent of all patients during the second and third week of the illness. Simultaneously, pro-

thrombin levels may be low, alkaline phosphatase levels high, and the levels of cholesterol esters and serum albumin both decreased.

COMPLICATIONS

The mortality rate from Virus A hepatitis is very low, being estimated at less than 0.2 per cent; that of the B type infection, however, has in some cases gone as high as 20 per cent. In one series of patients over 30 years old, hepatitis resulting from blood or plasma transfusions showed an over-all mortality rate of 30 per cent. When the hepatitis follows a fatal course it usually starts with restlessness, personality changes, delirium, convulsions, hemorrhages, ascites, edema, and coma. Massive doses of cortisone or ACTH have saved some lives in such emergencies, but information on that is still scanty.

MANAGEMENT OF THE DISEASE

The old Hippocratic tradition of letting nature take its course applies admirably to the management of both types of viral hepatitis. In fact, there is virtually nothing to do except to see that the patient gets some rest, does not contract a secondary infection, and takes in nourishment. If anorexia is severe, a 10 per cent glucose solution can be given parenterally. Antihistamines may help to reduce nausea. Antibiotics and lipotropic agents such as methionine are of no use at all, and the earlier practice of giving liver extract has been abandoned. When the patient is seriously ill and the serum albumin level is dangerously low, intravenous albumin may give temporary relief, the usual dose being 50 Gm. a day for about a week.

As for the nature of the diet and the value of bedrest, clinical experience is woefully contradictory. High protein and high fat diets have been empirically recommended, but in one controlled study, patients on such a "special" diet remained ill considerably longer than patients who ate what took their fancy. In another careful study, patients confined to strict bed rest improved no more rapidly than those who moved about at leisure. All that one can say is that there may be a slight advantage in a high-protein diet for Virus A cases, whereas in the Virus B type this is not only useless but may even be harmful.

EPIDEMIOLOGY*

How are these baffling organisms transmitted? Most of the evidence, and it is by no means conclusive, points to the fecal-oral route of transmission for Virus A. Epidemics of infectious hepatitis have been traced to the fecal contamination of water and food. Some epidemiologists believe that there may also be a respiratory method of spreading the disease, though until the organism is isolated this can obviously not be proven. There must clearly be some sort of person-to-person contamination, inasmuch as family and school epidemic outbreaks are commonly reported. The pleasant custom of kissing is not entirely exonerated for the time being.

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* For more complete clinical and epidemiologic data, see *Viral Hepatitis*, Public Health Service pub. No. 435, U. S. Dept. of Health, Education, and Welfare, Washington, D. C.

Infectious hepatitis can occur at any time of the year, although there is a fairly regular pattern of epidemic prevalence in the autumn and early winter, with a decline in the late spring and summer. In some areas the disease can be endemic without seasonal variation. In view of all this uncertainty, the only control measures that can be recommended are the obvious ones of good community sanitation and personal hygiene.

The epidemiology of Virus B hepatitis is not known. Some people without any symptoms at all can carry the organism around for as long as five years, and it is quite possible that they transmit it by close contact. On the other hand, none of the Virus B types have so far been demonstrated in stools or respiratory tract secretions. The usual form of transmission is thought to be through improperly sterilized instruments and blood or plasma transfusions. The safest measure is to refuse to accept blood for transfusion from anyone who has had jaundice in the past, however long ago. The various methods of "decontaminating" blood or plasma stores tried so far have been mostly ineffective.

As for the use of human gamma globulin in the prophylaxis of infectious hepatitis, it appears to have some value when given during the incubation period. But who knows exactly when the future sufferer is in the throes of incubation? Moreover, a person who derives some benefit from gamma globulin for himself, by enjoying a subclinical attack of the disease, will merrily go about his usual business and infect a large number of other persons with the viruses he carries. Which leads to the paradox that while gamma globulin may protect an individual, it can endanger a whole community.

Third Inter-American Congress of Psychiatry Holds Meeting in December

The Inter-American Society of Psychology invites its members to attend The Third Inter-American Congress of Psychology at the University of Texas on December 16–21, 1955. Psychology of Social Tensions, the central theme of this Congress, will be approached from the points of view of applied psychology, mental health, social anthropology and teaching. There will be four major symposia plus conferences, showings and discussions of films, and guided tours.

For information regarding membership in the Inter-American Society of Psychology, contact Dr. Werner Wolff (Secretary General), Bard College, Annandale-on-Hudson, New York.

To apply for participation in the December Congress send five copies of an abstract of approximately 250 words to the Program Committee, c/o Dr. Werner Wolff at the above address.

Clinical Data on Carbetapentane

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Cough is one of the symptoms about which the medical practitioner is most frequently consulted. Although cough can be evoked voluntarily in its spontaneous form, it is nevertheless a reflex action. It serves to expel from the bronchi accumulated mucus, foreign bodies, inflammatory products, and irritants.

It is not our intention to give an account of the mechanism or of the physiology of cough or to describe the various pathologic conditions with which it is associated, but to present some clinical results obtained in cases of allergic cough with the use of a new antitussive agent, carbetapentane (Toclase*†).

This type of cough is generally strident, dry, and tenacious, appearing whenever the patient comes into contact with the allergens to which he is hypersensitive. The cause of the cough-provoking irritation is probably a slight edema of the pharynx extending to the larynx and due to the antigen-antibody reaction. The diagnosis rests mainly on a precise history of the relationship between the appearance of the coughing fits and the contact with certain antigens, as well as on the results of skin tests.

Treatment consists essentially of removal of the causal antigen and of specific desensitization. Such treatment is important inasmuch as this type of cough is often the forerunner of bronchial asthma. Removal of the cough-provoking antigen, however, is not always possible, and desensitization does not always give the desired results; in such cases, symptomatic relief of the cough is necessary. Indeed, in contrast to bronchitis and other infective conditions in which coughing ensures expulsion of phlegm from the bronchi, the cough in these cases not only is unproductive, since there is little or no secretion, but also may give rise to much distress and to some harmful consequences. Morphine derivatives and codeine, which give symptomatic relief of cough, only partly solve the problem, entailing as they do the risks of habituation and harmful secondary effects such as constipation or anorexia that often occur as a result of prolonged treatment. For this reason we employed a new antitussive agent, carbetapentane, in our patients.

Animal experiments, using the method of Domenjoz, showed that carbetapentane is one and a half times more active than codeine phosphate and that it has a low toxicity. We tried this preparation in 14 patients with allergic cough, of which the following two case reports are typical.

Case 1: M.D., male, aged 38, who had been an upholsterer for 22 years. For the last five to six years he had suffered from a chronic, dry, tenacious cough, occurring chiefly during working hours.

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* The trade name of Chas. Pfizer & Co. for carbetapentane is Toclase.

† Available also from Union Chimique Belge, Brussels, as Tuclase.

During the two months previous to treatment he had experienced, on three occasions, a slight oppression in the chest accompanied by sibilant breathing. Several roentgenograms revealed no pathology apart from a slight emphysema. Previous therapy with an autogenous vaccine followed by a stock vaccine had effected no improvement. The administration of various types of codeine preparations had to be stopped after some time because of severe constipation. Skin tests showed a high sensitivity to domestic allergens. He was advised to change his occupation, but for various reasons this was not possible at the time. Desensitization with domestic allergens gave only a slight measure of relief, because the amounts of allergens to which he was daily exposed were massive. He was advised to take carbetapentane in a dosage of 22 mg. three times daily. The cough became appreciably less, and during the three and a half months in which he was under observation, he showed no manifestation of intolerance.

Case 2: M.V.D.M., a student aged 20, who for the past six years had suffered from hay fever from mid-April or mid-May until the end of July. In the last two years this had been complicated by a dry cough that interfered with his studies. Antihistamines gave only slight relief of the nasal symptoms and had no effect on the cough. Because it was too late at the time of consultation to institute desensitization therapy, he was treated symptomatically with antihistamines and carbetapentane in a dosage of 8 cc. three times daily. The latter gave distinct relief of the troublesome cough, and during the five weeks in which this case was followed up, there were no harmful secondary effects.

It is obviously impossible to express diminution of cough in the form of a statistical percentage, but in most of the cases, notable relief was obtained. Moreover, during the follow-up period, which varied from 4 to 18 weeks, in none of the patients were any manifestations of intolerance or harmful secondary effects observed.

The product was tried in 8 cases of chronic bronchial asthma. In contrast with the preceding group, the cough-provoking irritation was due to the sticky and viscous phlegm which adhered to the walls of the bronchi and could be expectorated only with much difficulty and by violent coughing. In view of the fact that carbetapentane exercises neither a bronchodilator action nor a liquefying effect on the bronchial secretions, in 7 of the 8 cases preference was given to preparations possessing these properties.

In cases of chronic allergic cough in which etiologic treatment is impossible or unsuccessful, carbetapentane is a useful aid in obtaining symptomatic relief. Moreover, it has the advantage over morphine and codeine preparations of not giving rise to harmful secondary effects.

Quarterly Review of

OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY

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FOREWORD

The objective of the QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, now incorporated in the INTERNATIONAL RECORD OF MEDICINE, is to bring together in one publication, in concise form, the essence of all that is published in otology, rhinology, laryngology, bronchology and esophagology from the world's voluminous literature, so that with a minimum of time and expense you are enabled to keep abreast of the rapid progress in these special fields of medicine and surgery.

The organization and simplification of the new data and the separation of the less significant findings from the important facts keep you continuously posted. The QUARTERLY REVIEW OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY brings you many new clinical discoveries—improved technics—world-wide research—a vast fund of important data, all in concise form.

The clinical facts presented here are systematically gathered from every available source. They are condensed from more than 300 medical and surgical periodicals, transactions and special publications and are properly classified and indexed for quick reference.

A section entitled "The International Record of Otorhinolaryngology and Bronchoesophagology" is included and consists of advanced experimental and clinical reports in otorhinolaryngology and bronchoesophagology.

Quarterly Review of **OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY**

Incorporating the International Record of Otorhinolaryngology and Bronchoesophagology

ABSTRACTS

otology

40. *A Primary Cholesteatoma of the Middle Ear.* KENNETH M. DAY, Pittsburgh, Pennsylvania. Ann. Otol., Rhin. & Laryng. *64*:161–163, March 1955.

A case is presented of a 45 year old woman with a cholesteatoma in the middle ear behind an intact ear drum. Symptoms of fullness and discomfort were present for only two months.

Examination revealed a distended drum with a beginning necrosis in the posterior quadrant. Roentgenograms showed normal, pneumatic mastoids with no pathological findings. An atticotomy was performed revealing a cholesteatoma which filled the middle ear. It was possible to remove the sac in toto except for a small area on the posterior wall of the middle ear around the pyramidal eminence from which the sac appeared to arise. The mastoid process was not opened. There was primary healing with no discharge. A small perforation of the drum occurred in the necrotic area. Hearing improved to a practical level in spite of the removal of the incus. The patient has been symptom-free for nine months. 1 figure.—*Author's abstract.*

41. *Labyrinthine Surgery in the Treatment of Ménière's Disease.* J. R. LINDSAY AND K. H. SIEDENTOP, Chicago, Illinois. Ann. Otol., Rhin. & Laryng. *64*:69–78, March 1955.

Labyrinthine surgery for Ménière's disease which has been done at the University of Chicago since 1940 is reviewed. Surgery was advised in less than 10 per cent of the cases.

Several techniques were used in the early cases in an attempt to destroy vestibular function while preserving hearing, but none of these were satisfactory. These

techniques included Portmann's operation on the saccus, simple fenestration, and fenestration of the horizontal canal at the ampulla with attempted intravestibular destruction of the superior division of the vestibular nerve with barbed dental broach. In two later groups, the coagulation technique recommended by Day and modified by Cawthorne's method of ablating the horizontal membranous canal was used with more consistent success. The experience with all groups was that while attacks of vertigo were prevented in nearly all cases, the hearing was always destroyed and the tinnitus was unchanged in a fairly large percentage. In an attempt to improve results a more radical technique was used in the last four cases. This consisted of a radical destruction of the ampullas of the horizontal and superior semicircular canals and exenteration of the contents of the vestibule. It was hoped that by a more complete destruction of the inner ear, the tinnitus would be relieved in a greater percentage of cases.

While the results of labyrinthine surgery are generally good in properly selected cases there are some patients who experience dizziness from head movements for as long as several years after the operation. This is attributed to the failure to develop adequate compensation. 18 references. 4 tables.—*Author's abstract.*

42. *External Umbo Blebs.* B. W. ARMSTRONG, Laryngoscope *65*:817 (Sept.) 1955.

This paper records observations on lipoid blebs at the umbo, an entity that is infrequently described, based on 24,000 office examinations during a five year period. In that series, blebs at the umbo were found in 66 ears, an incidence of 1:364. The external blebs were smooth, rounded, glistening intra-epidermal collections of clear, oil fluid, and were observed much more frequently than mucosal blebs. It was noted that definite symptoms were significantly absent in all cases. The author suggests that these noninflammatory blebs represent a localized degenerative process resulting in the dissolution of epithelial cells. Their etiology remains to be determined. The lack of symptoms possibly accounts for the fact that many otologists are unfamiliar with the existence of this type of bleb.

43. *Studies on Per-stimulatory Adaptation in Various Groups of Deafness.* TAUNO PALVA, Laryngoscope *65*:829 (Sept.) 1955.

The data given in this review for per-stimulatory adaptation in normal subjects suggest that the development of adaptation is not related to the intensity level, as far as the two sensation levels of 60 and 80 decibels are concerned. At these levels the adaptation loss was measured at 4,000, 2,000, 1000 and 500 cycles per second. The loudness level loss, measured after three minutes, continuous stimulation, was on an average less than 10 db. In 18 cases of conductive deafness and in nine ears with non-recruiting perceptive deafness, the adaptation loss was comparable to normal values. In recruiting perceptive deafness (51 ears) an abnormally large adaptation loss (30 db or more) was found in 14 per cent. It is concluded that abnormal loudness adaptation is not related to poor speech discrimination, and it does not occur as frequently as sometimes assumed.

rhinology

44. *Rhinology in Children. Resume of the Literature for 1954.* D. E. S. WISHART, J. B. WHALEY AND W. B. WALLACE, Laryngoscope *65*:735 (Sept.) 1955.

This comprehensive review of the literature (48 pp.) on the progress made in the treatment of rhinologic conditions in children comes from the Hospital for Sick Children in Toronto and the Department of Otolaryngology of the University of Toronto. The medical journals, including the pediatric publications of the United States, Britain and Canada are reviewed. The literature is classified under these main headings: general articles, sinusitis, bacteriology, drugs, antibiotics, congenital abnormalities, allergy, tonsils and adenoids, irradiation, tonsils and poliomyelitis, mouth and throat infection, and tumors. The most controversial question reviewed in the literature is the question of a possible relationship between tonsillectomy and poliomyelitis; authors of both the pro and the con schools being given adequate representation.

45. *Management of Allergic Sinusitis.* O. E. VAN ALYEA, Chicago, Illinois. Ann. Otol., Rhin. & Laryng. *64*:192–203, March 1955.

Successful management of allergic sinusitis is contingent upon close cooperation between the allergist and the rhinologist. Allergists, in treating respiratory allergy, are often prone to minimize the importance of rhinologic examination and therapy, and rely on elimination, injection, and antihistamine therapy despite the presence of polyps and symptoms referable to the sinuses, and similarly, otolaryngologists too often fail to realize the importance of the role played by allergy in the inception and maintenance of attacks of sinusitis.

Edema is the outstanding characteristic of allergy and its effects in rhinology are many-fold. Allergic edema and polyps block the nose and diminish the size of the sinus drainage outlets to a minimum thereby aiding in the inception and maintenance of attacks of sinusitis.

A wide variety of cases of allergic sinusitis is commonly observed but these roughly may be classified into five major clinical groups. (1) Acute suppurative sinusitis on an allergic basis. (2) Subacute sinusitis maintained by structural drainage barriers and allergic edema. (3) Acute and subacute sinusitis with drainage blocked by polyps. (4) Chronic sinusitis with edematous constriction of sinus outlet. (5) Chronic sinusitis with or without polyposis which has been subjected to one or more radical surgical procedures.

Treatment of the various types of allergic sinusitis is carried out in similar manner to that rendered in the nonallergic case with the goal of the rhinologist ever being the establishment of adequate sinus drainage passageways. 3 references. 6 figures.—*Author's abstract.*

laryngology

46. *Neurogenic Tumors of the Larynx.* GONZALO E. APONTE, AND ENRIQUE A. VICENS, Philadelphia, Pennsylvania. Ann. Otol., Rhin. & Laryng. *64*:319–325, March 1955.

A case of laryngeal neurilemmoma, the largest such neoplasm ever described in that site and the only case in which its removal necessitated a laryngectomy, is described. It occurred in a 39 year old white woman who complained of hoarseness and increase of dyspnea for four months. Roentgenograms disclosed a large cystic mass blocking the hypopharynx and displacing the epiglottis forward. Due to its encroachment upon the airway and extensive softening of the laryngeal and upper tracheal cartilages by the huge neoplasm, a laryngectomy was performed. Histologically, the tumor proved to be a neurilemmoma.

Five other cases of laryngeal neurilemmoma or neurofibroma are recorded in the last 25 years at the Jefferson Medical College Hospital. A review of the world's literature discloses 34 additional cases of neurogenic neoplasms of the larynx. Except for an equivocal case of ganglioneuroma, all were diagnosed as neurilemmoma or neurofibroma. Differentiation between the latter two entities is discussed. Twenty-four cases occurred in women, 12 in men, and in 3 the sex was not specified. The age of the patients ranged from 5 to 75 years. Hoarseness, the commonest manifestation, existed from a few months to 20 years prior to diagnosis. Sites of predilection were the aryepiglottic folds, ventricular bands, and true vocal cords. Six cases manifested disseminated neurofibromatosis. Recurrence of the tumor eventuated in one instance, and in another the lesion was fatal. Therapeutically, simple enucleation has been curative, but occasionally a laryngofissure or, as in our particular case, a laryngectomy has been necessary. 29 references. 2 figures.—*Author's abstract.*

47. *Pleomorphic Salivary Adenoma ("Mixed Parotid Tumour") of the Larynx.* BARBARA M. L. ABERCROMBY AND R. E. REWELL, Liverpool, England. J. Laryng. & Oto. *69*:424–429, June 1955.

A woman aged 33 years was thought to be suffering from "asthma" for four years. On examination of the larynx an ovoid tumour, 4 cm. by 3 cm. was found lying in it like an egg in an egg cup. Its removal removed the symptoms. The tumor was a pleomorphic salivary adenoma. Its structure did not help to decide whether such tumors come from the mucus-secreting glands of the mucosa or from its basal layer, but it was evidently of epithelial nature and there seemed no need to invoke the presence of ectopic salivary tissue for its development. Moreover, it showed stages in the development of "pseudo-cartilage" which are not usually evident. 3 references. 4 figures.—*Authors Abstract.*

bronchology

48. *Respiratory Disturbances in the Newborn and Young Infant.* ROBIN P. MICHELSON, Laryngoscope *65*:786 (Sept.) 1955.

Conditions in the newborn and young infant producing respiratory dysfunctions with or without anoxia are numerous, and often very complex. This discussion is largely limited to conditions in which abnormal structure or altered dynamics of the respiratory tract are chiefly at fault. It notes that atelectasis is the most frequent finding in neonatal death, while birth trauma and congenital defects are of lesser importance. Three types of conditions giving rise to tracheal obstruction in the infant are classified as intrinsic ones, usually produced by tumors and more rarely by congenital malformation; extrinsic lesions producing compression, commonly due to congenital cardiovascular defects; and collapse of the tracheal wall, associated with absent or defective cartilaginous tracheal rings.

This review also presents eleven cases of the syndrome of pulmonary hyalin membrane with resorption atelectasis treated by sternal traction. It is suggested that the movements of the thorax observed in "congenital flail chest" are persistent fetal respiratory movements; direct observations in support of this theory are, however, not presently available. A case report is included of agenesis, or failure, of pulmonary development, a rare occurrence.

miscellaneous

49. *Geriatrics of the Ear, Nose and Throat.* EDGAR E. POOS, Detroit, Michigan. Eye, Ear, Nose and Throat Monthly. *34*:315–319, May 1955.

At the present time 30 per cent of our population is over 45 years of age. At this age we enter an involution or catabolic state. Symptoms and signs of disease are much less conspicuous and people have a lessened tolerance to stress, have nutritional variations, may not digest food properly, often having a tendency to fixed habits, and often exhibit a feeling of insecurity or rejection.

The arterial system is affected by changes in the walls of the blood vessels and often increased pressures. There are disturbances of intracellular and extracellular dehydration or dessication fluid reduction and/or depletion and general cellular atrophy, particularly in the nervous skeletal and glandular elements and fibroses of interstitial connective tissue with hypertrophy or hyperplasia leading to degenerations.

External Ear. The skin becomes more flaccid, later becoming thin. There is a tendency to develop keratoses, lanugo hair becomes longer and stiffer like bristles, have less cerumen formation, often complain of senile pruritus. Presbycusis is the

most frequent cause of hearing impairment in advancing years. The onset is insidious and its progress slow. It is generally due to arteriosclerotic and degenerative changes within the inner ear. Tinnitus is common in older people, cardiovascular diseases, anemias, cerebral arteriosclerosis, allergy or toxic states and may follow use of drugs. Ménière's disease often starts in midlife, deafness and tinnitus often precede the onset of vertigo for some time. It is often due to vascular or degenerative changes in the internal ear.

Nose. Allergies, infections, and sinus diseases have a tendency to improve in older people due to fibrosis of the blood supply, atrophy of the mucous membrane, glands and tunica propria, causing increased ventilation, but they often complain of a dry nose and loss of smell. Epistaxis from hypertension and arteriosclerosis may be often be severe.

Mouth and Throat. Burning tongue, glossitis, pellagrous or riboflavin deficiency and leukoplakia are often present in the aged.

Larynx. Always be suspicious of prolonged hoarseness in older people. 5 references.—*Author's abstract.*

50. *Disturbances of Caloric and Optokinetic Nystagmus Associated with Localized Lesions of the Cerebral Hemispheres.* E. A. CARMICHAEL, M. B. DIX, AND C. S. HALLPIKE, London, England. J. Laryng. & Otol. *69*:269–276, April 1955.

Dusser de Barenne and de Kleyn (1923) demonstrated that the removal of one cerebral hemisphere in a rabbit led to a central facilitation of induced vestibular nystagmus with its rapid component towards the side of the lesion. These findings were later confirmed and extended to human subjects by Fitzgerald and Hallpike (1942) who found the same directional preponderance of caloric nystagmus to the side of the lesion in a number of cases of unilateral cerebral tumor. In addition, they were able to assign the locus of the mechanism responsible for this disturbance to the temporal lobe.

It has also been shown by Fox and Holmes (1926) that a unilateral cerebral lesion brings about a preponderance to the side of the lesion of another closely allied form of nystagmus, optokinetic nystagmus.

The authors have carried out observations of caloric and optokinetic nystagmus in 73 patients with unilateral cerebral lesions. They have shown that large lesions of the posterior parietotemporal region cause a directional preponderance to the affected side, both of caloric and optokinetic nystagmus.

The clinical findings which indicate that either of these derangements may occur independently suggests that separate centers exist in this area for the directional control of these two varieties of nystagmus. This suggestion is confirmed by the pathologic findings in cases in which one or the other of these derangements occurs alone. Thus the area concerned with caloric nystagmus is shown to lie in the posterior part of the temporal lobe, while that concerned with optokinetic nystagmus lies in the supramarginal and angular gyri. 3 references. 7 figures.—*Author's abstract.*

51. *The Early Diagnosis of Spinal Tumours.* H. J. G. BLOOM, H. ELLIS, AND W. B. JENNETT. Brit. M. J. *4904*:10–16, January 1, 1955.

Spinal tumors in their early stages often present a difficult diagnostic problem partly because the presence of such a lesion is comparatively rare and partly because it may simulate other more common disorders for many months or even years before there is total cord compression.

Late diagnosis may prove disastrous to the patient with a benign spinal tumor. Irreparable damage may occur either from prolonged compression of the cord or from interference with its blood supply, so that even if a total removal is still possible the recovery is slow and perhaps incomplete.

These comments on the early clinical picture and diagnosis of spinal tumors were based upon a study of 36 cases treated at the Military Hospital for Head Injuries, Oxford, between 1940 and 1951. There were 32 males and 4 females, the ages ranging from 17 to 60 years, 30 of them being under 35 years. The average delay between the first consultation and operation was 6.4 months, which is shorter than in most civilian series. Common diagnostic errors were "fibrositis" or "rheumatism" in 28 per cent of the cases, prolapsed intervertebral disk or "sciatica" in 28 per cent and "neurosis" in 25 per cent.

The most frequent complaint was backache and/or root pain which occurred in 81 per cent of the cases; in 61 per cent it was the initial symptom. In 5 cases there were only minimal or doubtful neurological signs although pain had been present for nine months or more.

The most frequent neoplasm was the neurofibroma (41 per cent). An unexpectedly large number of metastatic tumors was present (22 per cent), most of which appeared to be of bronchial origin; three of these tumors occurred in patients between 17 and 19 years of age. A metastatic lesion should be suspected if the history is short and the clinical picture advanced.

Reference is made to the ancillary investigations, and attention is drawn to the value of lumbar puncture in early diagnosis, especially in doubtful cases. Evidence of spinal block was obtained in 76 per cent of the cases, and in all 35 patients whose cerebrospinal fluid was examined the protein content was raised.

Lumbar puncture may be the only way of excluding a tumor with any confidence in patients with persistent back or root pain for which there is no obvious cause. The possible dangers of the procedure are negligible except in rapidly progressive cases, and those with suspected cervical tumors should have the investigation delayed until neurosurgical aid is available. 19 references. 3 tables.—*Author's abstract.*

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